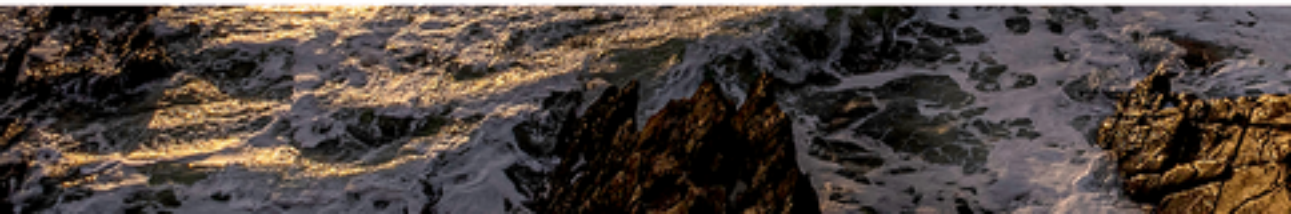


Palliative Medicine

A CASE-BASED MANUAL

FOURTH EDITION

EDITED BY
SUSAN MACDONALD | LEONIE HERX | ANNE BOYLE



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Foreword 1

In 1988 the Deans of 12 of the 16 Canadian medical schools at the time appointed representatives to a Canadian Palliative Care Curriculum Committee. In 1991 the Canadian curriculum was published and it became one of the first in the world, and the model for most medical schools globally. In 1997 the Canadian curriculum was updated, and at that time it was accompanied by a case-based manual. This manual was the template for the first edition of *Palliative Medicine: A Case-Based Manual* (1998). From its inception this book has been invaluable to a generation of medical students and clinicians worldwide.

The fourth edition has succeeded in keeping the user-friendly format with case presentations followed by questions and answers, updated to include all major new developments in the field. Drs. MacDonald, Herx, and Boyle have done an impeccable job at editing chapters written by a group of 57 authors from multiple regions, universities, and community programs in Canada.

This is a Canadian book from its very inception, and it emphasizes seamless and universal access to care across multiple settings, harmony between primary and specialist palliative care, and there is a refreshing lack of conflict of interest in all chapters. This book is, in my view, mandatory reading for all medical school students and junior graduates, as well as all clinicians who are likely to see seriously ill patients. Every chapter is self-standing, allowing clinicians to access chapters according to clinical need or interest.

Canadian physicians were pioneers in the development of palliative medicine. Against all odds they created clinical, educational, and research programs with great personal sacrifice. The medical school, health care systems, professional colleges, and hospital administrators were not as supportive of this very Canadian field of medicine, both in Canada and in most of the world. It is refreshing to read in this book the passion for the alleviation of suffering, the energy, and optimism of these 54 authors and three editors.

It is my hope that some copies of this wonderful book will get to the hands of many of the healthcare and academic leaders in Canada and other regions of the world, and that it will inspire them to create the structures and processes needed to implement all this knowledge, and prevent and alleviate suffering close to the end of our lives.

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Foreword 2

This lovely book captures the essence of palliative care: an approach to medical care that prioritizes relationships. Human connection. The use of stories to illustrate the human condition and what clinicians can do to alleviate suffering through presence, witness, and attention. The authors make clear that against the harshness of the world, relationships with other people gives meaning, connection, and purpose. The central principle of healing in health care is predicated on a foundation of relationship. More than any other text I've seen on palliative care, this work iterates and reiterates the power of human connection and the fact that it is prerequisite to accomplishing any of our good intentions in medicine.

It sometimes feels to me as if the practice of medicine, increasingly subspecialized and procedural and fragmented, has given up on the relationship between clinician and patient as old fashioned, as unnecessary, as too time consuming. The folly of that shortcut is made clear in this book. I hope it is read by people in training as well as those of us in the midst of our careers. It is about the fundamentals. We can all use the reminder and the guidebook.

Philosopher and ethicist David Barnard said it best: "*The sting of illness and death is the specter of broken relationships and the loss of the world. Over and against this threat stand the efforts of caregivers and companions to embrace the sufferer and continuously reaffirm his or her capacity for relationship.*" (Barnard D. The promise of intimacy and the fear of our own undoing. *Journal of Palliative Care* 1995;11, no. 4 (December): 22–26.)

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Preface

Palliative care is a dynamic and changing field. In the early days, when patients were reluctantly referred to us, we often had only days to grapple with challenging symptoms and overwhelming grief. Many patients were seen far too late for effective treatment and it was frustrating and disheartening. We knew our patients could have better care and we felt that they deserved it. As is common in such situations, leaders emerged within our small community of clinicians. They examined the questions we struggled with through a different lens and brought research methodology and scientific rigour to our everyday practice. They challenged us to try harder, try differently, do better, and be better. Slowly, but surely, things improved. We developed a body of knowledge that is evidence-based. We created tools for evaluation and measurement. We devised a curriculum for medical school learners and those already working in the discipline who sought a deeper understanding of our field.

Palliative care is moving into another new and exciting phase. We recognize the importance and benefit of all clinicians becoming equipped to provide a palliative approach to care, to see patients much earlier in the course of their illness, and to have access to specialist palliative care when needed. We have the opportunity to collaborate with our patients and interprofessional colleagues and create care plans that can provide significant positive benefits. Sometimes, those benefits can last for years. We have challenged our understanding of society, ethics, and the individuals we serve. We have expanded our horizons, both externally and internally.

This edition of *Palliative Medicine: A Case-Based Manual* is a response to the growth and constant evolution in such a challenging and dynamic field. While change is not always comfortable, it is inevitable. We, the Editors, have taken the opportunity to review what is currently known and to consider what is new and developing. We have included a few new chapters—apps and websites, structurally vulnerable populations, for example. We have placed more emphasis on non-oncological conditions as palliative care continues to expand into this domain.

For the purpose of this textbook, the term family refers to whatever community or individuals the patient has chosen to be their primary support. As well, there may be unique cultural and/or spiritual considerations that will need to be taken into consideration for the care of individual patients. Readers are also encouraged to always review and double-check all medications (and look for possible interactions/allergies) for an individual patient before prescribing.

As Editors, we wish to gratefully thank our wonderful authors, who diligently laboured through numerous revisions with grace and good humour. It was a joy to work with all of you. We wish to thank our families, who good-naturedly abided while we learned how to put together this manual. We are also very grateful for the constant guidance and support by our Oxford colleagues, Janine and Caroline.

Despite all the advances, changes in nomenclature, and things that go in and out of vogue, one thing will remain—palliative care clinicians value person-centred care to relieve suffering. We see the importance of quality of life. We accompany our patients and families in their most difficult

times. We are aware that the most important therapeutic intervention we have is the relationship we create with our patients and the culture of caring we establish. For that reason, we wish to take this opportunity to thank our patients. It is a privilege and honour to serve and we are deeply indebted to them. As William Osler said, the best medical education 'begins with the patient, continues with the patient and ends with the patient'.

Susan
Leonie
Anne

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Chapter 1

Advance care planning and goals of care discussions

Jeff Myers and Jessica Simon

Attitude

To enable each learner to:

- Reflect on the need to approach advance care planning (ACP) with an open mind, to explore each person's values without judgement.
- Recognize one's own biases, including medical culture, that impact how one conducts conversations and makes recommendations about treatment plans.

Skills

To enable each learner to:

- Utilize four key elements of ACP: (1) helping patients identify a substitute decision-maker and reflect on their own values and priorities; (2) exploring illness understanding and sharing prognosis tailored to patients' readiness; (3) eliciting patient values and priorities; and (4) documenting conversations and helping patients communicate their plans.
- To integrate knowledge of a patient's values, and social and medical context to make recommendations around medical decisions.

Knowledge

To enable each learner to:

- Recognize which components of ACP are jurisdictional and which might be applied universally.
- Describe common barriers and facilitators to ACP and goals of care (GOC) conversations.
- Summarize the limits of current evidence about the impacts of ACP at the level of healthcare systems.

Case 1.1

G.S. is a 68-year-old man of South Asian ethnic origin and Sikh faith. He was born in Uganda and moved with his family to Canada in 1972. Trained as a civil engineer, in Canada, he worked in the railways until his retirement 3 years ago. He lives with his wife and 92-year-old mother. He has four adult children, three of whom live locally and one in the United States. He has no previous experience of making medical decisions for others and his father died suddenly from a heart attack aged 73 years. He has a will and documents related

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to financial decision-making, naming his oldest son, in the event he loses capacity, but no documents related to medical decision-making. He has type 2 diabetes and hypertension, with mild to moderate end-organ damage, evidenced by chronic renal impairment [glomerular filtration rate (GFR) 55] and pre-proliferative retinopathy.

Question 1. What is advance care planning (ACP) and why would G.S. benefit from starting ACP?

There are two similar international consensus definitions of ACP. One, from predominantly North American perspectives,[1] defines ACP as, 'a process that supports adults at any age or stage of health in understanding and sharing their personal values, life goals, and preferences regarding future medical care. The goal of advance care planning is to help ensure that people receive medical care that is consistent with their values, goals and preferences during serious and chronic illness.' The second, supported by the European Association of Palliative Care,[2] provides an extended definition:

> 'ACP enables individuals who have decisional capacity to identify their values, to reflect upon the meanings and consequences of serious illness scenarios, to define goals and preferences for future medical treatment and care, and to discuss these with family and healthcare providers. ACP address's individuals concerns across the physical, psychological, social, and spiritual domains. It encourages individuals to identify a personal representative and to record and regularly review any preferences, so that their preferences can be taken into account should they at some point be unable to make their own decisions.'

At the heart of both definitions of ACP is an iterative communication process—talking to those close to us and to healthcare providers about our wishes and values, particularly in relation to our health, and revisiting the topic over time. This process prepares people for in-the-moment decision-making,[3] either as patients themselves or as representatives or 'surrogate decision-makers' of the patient who has lost capacity. In many jurisdictions, written communication is also legally recognized, where a person can appoint someone who will have the authority to participate in medical/personal decision-making on their behalf, and in some jurisdictions, written instructions or guidance can be left for that decision-maker. ACP has been recognized as an important component of person–family-centred care and preparation for shared decision-making, and a key supportive process in a palliative approach to care.[4] ACP balances a 'transactional' model of medical care—'What's the matter with you?'—and a 'personal' model of medical care that asks, 'What matters to you?'[5]

Benefits to the person include peace of mind in having their wishes known and a higher likelihood of receiving goal-concordant care. Surrogate decision-makers and family members may benefit from feeling they have honoured the person's wishes and ACP is associated with less severe stress, depression, and anxiety in bereavement.[6] However, systematic reviews have found mixed results,[7] and effective ACP interventions and appropriate outcome measures for ACP are still being defined.[8]

ACP can be considered for all competent adults. G.S. may benefit from ACP specifically because he has chronic illnesses which put him at increased risk of an incapacitating event; he has several family members who may or may not share a common perspective of his values, and he may have values unfamiliar to his healthcare team, potentially putting his family at risk of distress or discord during times when he is ill.

Question 2. How do the outcomes of an ACP conversation with a healthy person differ from one with a person who has a serious illness?

For healthy adults who have not had experience of being in the role of substitute decision maker, ACP can be an unfamiliar and abstract concept. Around 50% of Canadians report having had conversations with a family member or close friend regarding their healthcare treatment preferences in the event of serious illness or injury, but the depth of these conversations is unknown, and many fewer (around 10%) have spoken with a healthcare provider.[9] Talking with a healthcare provider can enhance understanding of:

1. The benefits and relevance of ACP to the healthy person and those close to them—for example, in the event of accidents with younger adults and sudden illness, like strokes, with older adults.
2. The characteristics of a suitable surrogate decision-maker—for example, the ability to make decisions under stressful circumstances, to be able to communicate with healthcare providers and be trusted to respect the extent or degree of flexibility the person wants them to exercise in representing their values.
3. The local legal documents and process for ACP.

In contrast, for people living with a serious illness, an ACP conversation also explores illness understanding, information preferences, sharing an individualized prognosis, and anticipating the kinds of decisions a person may face in the future and that may influence their care plan.[10] In both contexts, a positive outcome is that the person is activated to continue to talk about their wishes and that they feel heard and understood by those close to them and their clinicians.

Question 3. How might you introduce ACP to G.S. and assess his readiness level?

When introducing ACP, it might help to normalize this as a helpful process that you encourage participation in for all your adult patients.[10] Framing ACP as a part of living well may help to reduce patient anxiety.[11] This is particularly important as often ACP is confounded with end-of-life care and making decisions about death. Many health regions or countries have ACP resources that you can share with patients (see Box 1.1). Simple healthcare provider actions, like opening the resource (whether online or in print) and highlighting relevant sections, increase the chance that a person will review the material on their own, compared to passive sharing of resources.[12]

Box 1.1 Examples of national, English-language, online resources

Australia: http://www.advancecareplanning.org.au
Canada: www.advancecareplanning.ca
New Zealand: https://www.hqsc.govt.nz/our-programmes/advance-care-planning/
Singapore: https://www.livingmatters.sg/
United Kingdom: http://www.goldstandardsframework.org.uk/cd-content/uploads/files/ACP/Planning-for-your-future-care_patient-leaflet.pdf
United States of America: www.theconversationproject.org

Table 1.1 ACP readiness and clinician actions organized by the Stages of Change[16,17]

Stage	What the patient knows or is doing about ACP	Healthcare provider action	Sample questions
Pre-contemplative	Patient does not know about or has not considered ACP	◆ Introduce ACP and offer educational material ◆ Indicate questions or concerns about ACP can be addressed in future visits	◆ *How much have you heard about advance care planning?* ◆ *Have you had to make medical decisions before for someone close to you?*
Contemplative	Patient may be aware of ACP but is not ready to take any action	◆ Ask about questions or concerns related to ACP ◆ Offer resources that would assist identifying values or wishes ◆ Talk about the role and importance of the SDM	◆ *How do you and your family approach making medical decisions?* ◆ *What fears or concerns do you have*?
Planning/preparing	Patient reviews ACP educational materials or discusses the topic of ACP	◆ Ask about who they are planning to ask to be their SDM ◆ Discuss how to include family and SDM in discussions	◆ *If, at some point, you are unable to speak for yourself, who should speak for you about healthcare decisions?* ◆ *Does this person know and understand this responsibility?*
Action	Patient knows who their SDM is, has begun to discuss wishes, values, and beliefs, and may request help or further clinical information	◆ Offer to meet with patient and the SDM(s) to facilitate ACP conversation ◆ Offer to review their ACP documentation in relation to their health context	◆ *Do you have a [legal document in use in your jurisdiction]?* ◆ *Would you like to know more about the potential choices you may be asked to make, and what the benefits and burdens of those choices might be for you?*
Maintenance	Patient may seek confirmation of their plan and when to review it	◆ Periodically review and discuss ACP, particularly with a change in patient's health status, or critical illness of family member or friend, or if their SDM changes	◆ *Would you like to review your plan to see if it reflects your current wishes clearly?* ◆ *If your health condition or wishes change, it may be important for you to review your plan.*

ACP, advance care planning; SDM, substitute decision-maker.

Source: data from Westley C & Briggs L. 'Using the Stages of Change Model to Improve Communication About Advance Care Planning'. Nursing Forum 2004, 39(3).[13]

Rizzo V *et al*. 'Use of the Stages of Change Transtheoretical Model in End-of-Life Planning Conversations'. Palliative Medicine 2010, 13(3).

There are modifiable and non-modifiable factors that influence engagement in ACP;[13] at a personal level, these include age, socio-economic factors, and socio-cultural factors, including inequitable access to the medical or legal system. In addition, engagement in ACP is impacted by healthcare provider factors, such as their skill and comfort discussing ACP, and system challenges impacting available time, prioritization of ACP conversations, and document portability. There are research tools[14,15] to quantify ACP readiness and assess a person's stage in behaviour change, but in the absence of a standard clinical tool, one can explore readiness by inquiring about how G.S. and his family members prefer to plan for medical decisions. Asking what estate and financial planning the person has done, and in G.S.'s case commending him for his financial preparedness and looking after his family by having a will, can lead into explaining how ACP is the equivalent gift for his family in reducing distress around future medical decision-making (see Table 1.1 for examples of framing readiness for ACP by theoretical stages of change and the potential clinician actions at each level). These inquiries can segue the healthcare provider into further exploratory questions, defining ACP and discovering potential challenges for the person (e.g. having no trusted family member or friend to select as a surrogate), and suggestions for ACP activities (e.g. talking together with loved ones at a family meal, using an online guide, or attending a group workshop).

Case 1.1 (continued)

At age 76, G.S. has an ST elevation myocardial infarction and he is admitted to a coronary care unit. Post-angiography, he is in delirium with severe hypotension and acute kidney injury. His wife and children take turns being at his bedside 24 hours each day. His medical team wants to know about previous ACP conversations he has had and who they should talk to about medical decision-making regarding the potential use of intensive care, cardiopulmonary resuscitation, and intubation. At some point in the past, G.S. wrote down some of his wishes by stating, 'I do not want heroic or life support measures if I have an illness that is likely to leave me unable to recognize my family or be able to live at home with them.' His son is the named 'substitute decision-maker', but each family member has strong and differing opinions about what G.S. would and would not want in the face of this serious illness and the uncertainty about his functional recovery. His son is struggling to guide the healthcare team about his father's wishes.

Question 4. Will the ACP information help G.S.'s son with decision-making?

To address this question, we must first look at how medical decisions are made. There is a vast body of literature addressing the complex process of medical decision-making and for our purposes, the focus will be on basic information sources.[18]

There is widespread agreement that a decision about a treatment for a specific illness requires a patient to understand information about both their illness and its treatments. It can be problematic, however, if clinicians solely focus on these elements. When making medical decisions, illness and treatment-related information broadly comprise only one of two critically important sources of information (see Figure 1.1).

The second information source, one that is equally as important, is from the patient.[20] This information is values-based (i.e. what a person finds important in life and why this is important). When decision-making, solely focusing on information that addresses illness and its treatments risks taking the person out of the equation.

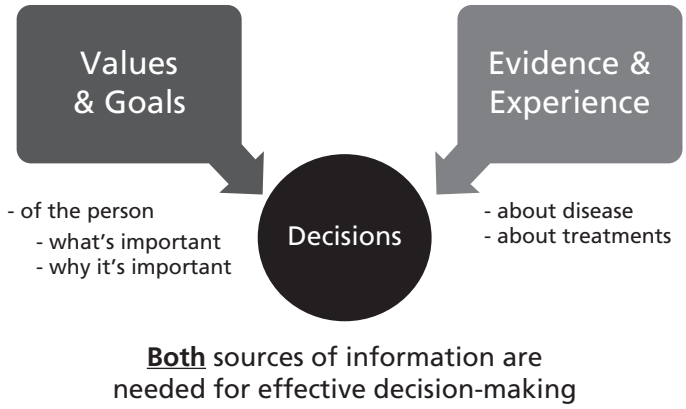


Fig. 1.1 Broad information sources critical for medical decision-making.[19]
Adapted courtesy of Dr. Nadia Incardona. Michael Garron Hospital, Toronto, Canada. Data originally from Fulford KWM, Peile E, Carroll H. 'Essential values-based practice: Clinical stories linking science with people'. New York: Cambridge University Press 2012.

When facing decisions, substitute decision-makers need to draw from previous ACP conversations for guidance. When first developed, the tasks of ACP comprised primarily completing an advance directive or living will that outlined the treatments a person would or would not want in the future.[3] This approach was found to be largely ineffective, however.[21,22] What was learnt from patients and decision-makers was that when it comes time to make complex decisions, information about specific treatment preferences can be difficult to interpret and apply.[23,24,]

An example is found with the first part of G.S.'s ACP information, 'I do not want heroic or life support measures'. In the past, this was commonly used as a standalone statement in ACP conversations but is difficult to interpret in the absence of further clinical context. An important reason for this is that patients do not value specific treatments themselves; they value the outcome of treatments.[23] Specific treatment preferences then may not be helpful information for substitute decision-makers.

Information that is likely to help substitute decision-makers could apply to a range of clinical contexts and includes the underlying reasons a patient has for a specific treatment preference (e.g. why a person does not want heroic or life support measures). As well, helpful ACP conversations include a patient's description of life circumstances considered to be acceptable and unacceptable, or tolerable and intolerable.

The resulting focus for ACP has shifted over the last several years, away from eliciting preferences for treatments and towards an emphasis on a person's values.[21,25,22] As to whether or not the ACP information outlined by G.S. will help his son with decision-making, it is likely to be partially helpful but will require the skilful facilitation of a GOC discussion.

Question 5. What are goals of care (GOC) discussions?

A proposed literature-derived definition for the phrase 'goals of care' is, '… the overarching aims of medical care for a patient that are informed by patients' underlying values and priorities, established within the existing clinical context, and used to guide decisions about the use of or limitation(s) on specific medical interventions.'[26] A person-centred approach involves setting out to understand who the person is, how they view their own clinical picture, and how their values and goals align with both the clinical picture and treatment approaches being considered.

Considerable focus is on assessing illness understanding, meeting information needs, and determining how the person defines and describes the goals they have for their care (i.e. being able to do or experience something).[27] From this point, the clinician and patient/decision-maker can determine the treatment and care that best fit with the person's goals. Approached in this way, the GOC discussion may illuminate misinformation and misunderstandings, as well as goals that are incongruent, or even incompatible, with the clinical picture. Additional time and multiple interactions may be necessary to adequately meet information needs and address the broad range of emotional responses that can occur.[28]

A component of the GOC discussion that is important to highlight is *illness understanding*. A patient can contemplate their values, as well as identify and prioritize their goals for their care, only once they understand individualized illness-related information relevant to their current context.[29] Currently, many patients with serious illness do not fully appreciate or understand their illness as being incurable and progressive.[30,31] This means a very high likelihood that a patient's/decision-maker's treatment and care decisions may not have been adequately informed. Examples of contributing factors to this include adequate information not being provided, information not being understood by patient/decision-maker, personal coping mechanisms that defer contemplating illness severity, and cultural barriers averting a person from conceiving of the illness trajectory.

Studies addressing information needs related to illness understanding have consistently reported that patients desire detailed information, certain types of information (e.g. quantitative or qualitative), and information that is both optimistic or hopeful and realistic or practical.[32,33,] Information needs vary greatly between patients and over time, which highlights the importance of iteratively readdressing. To effectively meet a person's information needs, the content and function of the information, as well as the best method of providing the information, are determined through a process of assessing what the patient knows, what he or she believes they need to know, and how the information might facilitate goal identification and decision-making.[34]

Another important component of the GOC discussion and a key element of meeting information needs is *prognosis*. This includes a description of the disease course and the possible impact of both the disease and the treatments being considered. Prognosis is often characterized as concrete information to be disclosed or considered synonymous with a survival estimate. 'How much time a person has left' is only one component of what prognosis broadly encompasses.[35] The main problem with a survival estimate is the high likelihood of inaccuracy and the risk this carries as far as how this information could be used by patients and families. If asked for a survival estimate, exploring the underlying reasons for the question, rather than simply providing a specific time frame, may lead to a far more effective interaction.

A general clinical and stepwise approach to the GOC discussion is outlined in Figure 1.2. Given the context for a GOC discussion is needing to make a treatment or care decision, the clinician's

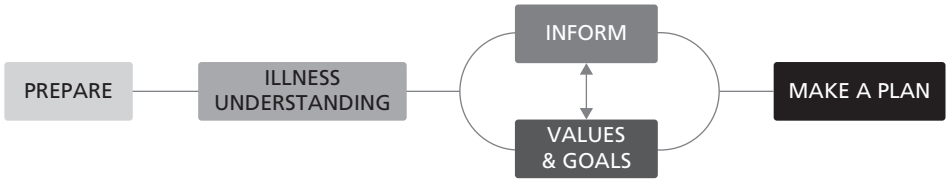


Fig. 1.2 Model for facilitating a Goals of Care Discussion.[36]

Reproduced with permission from Steinberg L, Soong C, Safavi N, Daly A. 'Improving your goals of care conversation'. Sinai Health System. 2019. Available at: http://www.goalsofcaremodule.com (Accessed Sept 29, 2019) (34).

aim should be to arrive at a recommendation that aligns with the patient's goals. The final step 'make a plan' is intentionally broad to encompass a wide range of possible plans. Examples of plans include a proposed treatment being recommended and a subsequent plan for informed consent or the plan of pausing the discussion to allow information to be digested.

Question 6. How can a focus on treatments be problematic and how can we support G.S.'s son and his family in medical decision-making at this time?

To review G.S.'s current status, family members have strong and differing opinions on what he would and would not want, which has left his appointed decision-maker, his son, uncertain with how to guide his father's care team. This is an example of the problems that can arise when ACP conversations primarily focus on treatments. We have outlined above other potential challenges with a treatment focus during ACP conversations and for the GOC discussion. Box 1.2 outlines the risks of using a treatment-centred approach.

G.S. has previously stated if he has an illness that is likely to leave him unable to either recognize his family or live at home, he would not want heroic or life support measures pursued. The most helpful information here is that he highly values both being able to recognize his family and being able to live at home. It can be inferred that G.S. would consider not being able to do these two things as unacceptable or intolerable. Examples of strategies that could be used to address the current decision-making challenges would then include:

- Instead of providing detailed information about treatments, focus discussions on who G.S. is, what he values, and what is important to him.
- To address differing opinions on what G.S. would want or not want, turn the question around by asking family members what they most hope for and most fear.
- When providing information and when engaging in decision-making processes, frame information using G.S.'s wishes (i.e. the likelihood he will be able to both recognize his family and live at home).

To describe a specific approach to decision-making that could be used with G.S.'s substitute decision-maker, consider the following scenario … *what would you do?*

Box 1.2 Risks of a treatment-centred approach to GOC discussions

- Greater likelihood medical jargon will be used and require patients to think of life in narrow, potentially unfamiliar medical parameters [e.g. cardiopulmonary resuscitation (CPR), bilevel positive airway pressure (BiPAP), transfusions, etc.][37]
- Erroneously assuming patients have adequately informed preferences for treatments[38]
- Interpreting treatment decisions documented as reflecting more than the specific decision (e.g. no CPR being equated with 'no interventions')[39]
- Inadequately recognizing the pressures on family members, who may be processing medical information, their sense of duty to protect their loved one, and their emotions of worries, fears, sadness, and hopes[40,41,41]

You have been diagnosed with a life-threatening illness and medication A is the only treatment that slows progression of the illness. For most people, however, medication A also causes at least a 25% loss in cognitive function.
Would you take medication A?

Clinicians in the role of the patient for this scenario will value cognition and longevity in highly individualized ways. A decision about *medication A* likely begins with consideration of what life with 25% less cognitive function would look like. This might include reflecting on questions like 'Could I work?', 'Could I still enjoy time with family and friends?', or 'How much of a burden would this be for others?'. The resulting image would then be compared with a life that is considered acceptable or tolerable. For some, a loss of cognition is an acceptable trade-off for greater longevity, and for others, the illness consequences are more acceptable than the risk of losing cognition. Regardless, a decision is made by applying what is considered acceptable or tolerable (i.e. what is valued and considered important). When a patient who is not a clinician is presented with this same scenario, most are likely able to describe an image of life considered acceptable or tolerable. It is unlikely, however, that a patient will be able to generate a realistic image of what life with 25% less cognitive function would look like. For G.S. then, he has described the conditions he considers intolerable and decisions are ideally framed around the potential impact on his abilities to recognize family and live at home.

To summarize this section, qualitative evidence from patients with serious illness outlines their view that the potential outcomes of treatments are more likely to matter than the treatments themselves. When discussing treatment options for specific diseases, to the extent possible, clinicians should spend time describing an image of what life may look like. This image can then be compared with what is considered acceptable or tolerable by the patient/decision-maker.

Case 1.1 (continued)

G.S. recovers to be discharged from hospital, but with a reduced left ventricular ejection fraction, chronic heart failure, and a GFR of 15. He is able to go home, but because he needs one person to assist with transfers and has a raised risk of falls with persistent hypotension, he requires 24-hour care and supervision. His prognosis appears to be many months or short years, with the potential for increasing frailty and recurrent episodes of acutely symptomatic heart failure. Although his delirium has cleared, he has associated cognitive changes such that he is slower to respond to questions. Cognitive testing finds reduced short-term memory and mild reductions in executive functioning. Overall, however, he has regained decision-making capacity, which comes as a relief to his son who struggled with decision-making throughout his father's hospital admission.

Question 7. How could you support G.S.'s ongoing ACP and expression of his priorities and goals for his care?

There are several ways to longitudinally support person-centred decision-making for G.S. and include awareness that life priorities will iteratively evolve, preparing G.S.'s son and entire family for future decision-making and documentation of ACP and GOC discussions over time.

As long as a patient has the capacity and readiness to participate, ACP conversations should occur iteratively and ideally revisited several times throughout the course of serious illness.

Examples of milestones warranting ACP conversations include involvement of any new care team, recent discharge from acute care, initiation of homecare, or a change in care setting. These bring important opportunities to ensure ongoing illness understanding and that information and emotional needs are being met, both for patients and substitute decision-makers.

The progressive nature of these illnesses means that over time, patients/decision-makers will have more and more clinical context from which to draw when making decisions. As illness progresses, priorities often shift, and both wishes and goals tend to evolve. If ACP is not routinely revisited or if the focus of GOC discussions is not person-centred, these shifts and evolutions may not be explored.

A specific circumstance important to capitalize on occurs when a decision-maker has temporarily been in the position of making decisions because the patient has been transiently incapacitated. Facilitating a discussion about the experience between the now capable patient and decision-maker could be tremendously valuable. Such a discussion could address:

- Confirming with the patient that the decisions were made 'fit' with their values.
- Discussing if and how wishes or goals have evolved for the patient.
- Assessing for distress among decision-makers around that decision-making process.
- Exploring the information that would further prepare decision-makers for the future.

Finally, ensuring effective documentation of any element of ACP and GOC discussions can be of substantial support to patients and decision-makers.[42] Although the aim for ACP is to prepare for 'in-the-moment' decision-making, accessible documentation of previous ACP and GOC discussions enables participants to build on prior conversations, rather than being initiated from scratch time and again.

Although documentation can help when measuring the effectiveness of ACP and GOC discussions, for these communication tools to meaningfully impact the care of a population, it is crucial to think beyond singular ACP and GOC elements. Improving patient and decision-maker outcomes is only likely to be achieved with broad commitments to integrating ACP and GOC discussions as part of routine care.[43] A comprehensive approach to this integration includes collaborative community engagement, medical and legal professional education, development of standard practices, monitoring and enhancing these practices through quality improvement, supporting policies, and digital infrastructure for documentation[43] Supporting the exchange of clinical information involves system-level coordination and planning.

Question 8. What is the impact of ACP at the *health system* level?

Systematic reviews looking at the impact of ACP suggest some impacts on the health system usage such as decreased life-sustaining treatment and hospitalization and increased use of hospice and palliative care.[7] It appears that legal directives alone have less impact than interventions that include broader ACP processes and communication. Although it is commonly stated that ACP may have positive health economic consequences, there are limitations with the current literature.[42] Prior studies are heterogeneous for health sectors, and the methods of valuation, including length of time prior to death, and intervention costs have not been reported. ACP might also help reduce healthcare provider moral distress and conflict, which could help with staff resilience and retention. In addition to any potential system impacts, ACP remains important as an ethical process for communicating and integrating persons' own values with medical decision-making.

References

1. **Sudore RL**, **Lum HD**, **You JJ** *et al*. (2017) Defining advance care planning for adults: a consensus definition from a multidisciplinary Delphi panel. *J Pain Symptom Manage*, **53**(5), 821–32.e1.
2. **Rietjens JAC**, **Sudore RL, Connolly M** *et al*. (2017) Definition and recommendations for advance care planning: an international consensus supported by the European Association for Palliative Care. *Lancet Oncol*, **18**(9), e543–51.
3. **Sudore R, Fried T** (2010) Redefining the 'planning' in advance care planning: preparing for end-of-life decision making. *Ann Intern Med*, **153**(4), 256–61.
4. **Hoerger M, Greer JA, Jackson VA** *et al*. (2018) Defining the elements of early palliative care that are associated with patient-reported outcomes and the delivery of end-of-life care. *J Clin Oncol*, **36**(11), 1096–102.
5. **Thomas K** (2012) Overview and introduction to advance care planning. In: Thomas K, Lobo B, and Detering K (eds.) *Advance Care Planning in End of Life Care*, 2nd edn, p. 12. Oxford University Press, Oxford.
6. **Detering KM, Hancock AD, Reade MC, Silvester W** (2010) The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. *BMJ*, **340**, c1345.
7. **Brinkman-Toppelenburg A, Rietjens JA, van der Heide A** (2014) The effects of advance care planning on end-of-life care: a systematic review. *Palliat Med*, **28**(8), 1000–25.
8. **Sudore RL, Heyland DK, Lum HD** *et al*. (2018) Outcomes that define successful advance care planning: a Delphi panel consensus. *J Pain Symptom Manage*, **55**(2), 245–55.e8.
9. **Teixeira AA, Hanvey L, Tayler C; Canadian Researchers at End of Life Network (CARENET)** (2015) What do Canadians think of advanced care planning? Findings from an online opinion poll. *BMJ Support Palliat Care*, **5**(1), 40–7.
10. **Bernacki RE, Block SD; American College of Physicians High Value Care Task Force** (2014) Communication about serious illness care goals: a review and synthesis of best practices. *JAMA Intern Med*, **174**(12), 1994–2003.
11. **Bernacki R**, **Paladino J, Neville BA** *et al*. (2019) Effect of the Serious Illness Care Program in Outpatient Oncology: a cluster randomized clinical trial. *JAMA Intern Med*, **179**(6), 751–9. doi: 10.1001/jamainternmed.2019.0077
12. **Harwood J, Gravenstein S**, **Kennelty KA**, **Loeckenhoff CE** (2012) *Communicating with older adults: an evidence-based review of what really works*. **The Gerontological Society of America**. https://www.geron.org/publications/communicating-with-older-adults
13. **Lovell A, Yates P** (2014) Advance care planning in palliative care: a systematic literature review of the contextual factors influencing its uptake 2008–2012. *Palliat Med*, **28**(8), 1026–35.
14. **Sudore RL, Heyland DK, Barnes DE** *et al*. (2017) Measuring advance care planning: optimizing the advance care planning engagement survey. *J Pain Symptom Manage*, **53**(4), 669–81.e8.
15. **Kassam A, Douglas ML, Simon J** *et al*. (2017) Behaviors in Advance Care Planning and ACtions Survey (BACPACS): development and validation part 1. *BMC Palliat Care*, **16**, 56.
16. Westley C Briggs L (2004) Using the stages of change model to improve communication about advance care planning. *Nursing Forum*, **39**(3).
17. Rizzo V *et al*. (2010) Use of the stages of change transtheoretical model in end-of-life planning conversations. *Palliative Medicine*, **13**(3).
18. **Joseph-Williams N, Elwyn G, Edwards A** (2014) Knowledge is not power for patients: a systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. *Patient Educ Couns*, **94**, 291–309.
19. **Fulford KWM**, **Peile E, Carroll H** (2012) *Essential Values-Based Practice: Clinical Stories Linking Science with People*. Cambridge University Press, New York, NY (adapted by Dr Nadia Incardona, University of Toronto).
20. **Williams I, Brown H, Healy P** (2018) Contextual factors influencing cost and quality decisions in health and care: a structured evidence review and narrative synthesis. *Int J Health Policy Manag*, **7**(8): 683–95.

21. **Perkins HS** (2007) Controlling death: the false promise of advance directives. *Ann Intern Med*, **147**, 51–7.
22. **Lum HD, Sudore R, Bekelman DB** (2015) Advance care planning in the elderly. *Med Clin North Am*, **99**, 391–403.
23. **Fried TR, O'Leary JR** (2008) Using the experiences of bereaved caregivers to inform patient- and caregiver-centered advance care planning. *J Gen Intern Med*, **23**, 1602–7.
24. **McMahan RD**, **Knight SJ, Fried TR, Sudore RL** (2013) Advance care planning beyond advance directives: perspectives from patients and surrogates. *J Pain Symptom Manage*, **46**, 355–65.
25. **Sudore RL, Fried TR** (2010) Redefining the 'planning' in advance care planning: preparing for end-of-life decision making. *Ann Intern Med*, **153**, 256–61.
26. **Secunda K**, **Wirpsa MJ**, **Neely KJ** *et al.* (2019) Use and meaning of 'goals of care' in the healthcare literature: a systematic review and qualitative discourse analysis. *J Gen Intern Med*, **35**, 1559–66. https://doi.org/10.1007/s11606-019-05446-0
27. **Frey MK, Philips SR, Jeffries J** *et al.* (2014) A qualitative study of ovarian cancer survivors' perceptions of endpoints and goals of care. *Gynecol Oncol*, **135**(2), 261–5.
28. **Dunlay SM, Strand JJ** (2016) How to discuss goals of care with patients. *Trends Cardiovasc Med*, **26**, 36–43.
29. **Myers J** (2017) Measuring quality of end-of-life communication and decision-making: do we have this right? *CMAJ*, **189**, E978–9.
30. **Weeks JC, Catalano PJ, Cronin A** *et al.* (2012) Patients' expectations about effects of chemotherapy for advanced cancer. *N Engl J Med*, **367**, 1616–25.
31. **Lefkowitz A, Henry B, Bottoms J** *et al.* (2016) Comparison of goals of care between hemodialysis patients and their health care providers: a survey. *Can J Kidney Health Dis*, **3**, 1–10.
32. **Innes S, Payne S** (2009) Advanced cancer patients' prognostic information preferences: a review. *Palliat Med*, **23**, 29–39.
33. **Howlett J, Morrin L, Fortin M** *et al.* (2010) End-of-life planning in heart failure: it should be the end of the beginning. *Can J Cardiol*, **26**, 135–41.
34. **Myers J, Selby D** (2014) Personalizing prognosis in a patient with serious illness. *CMAJ*, **186**, 169–70.
35. **You JJ, Fowler RA, Heyland DK** (2014) Just ask: discussing goals of care with patients in hospital with serious illness. *CMAJ*, **186**(6), 425–32.
36. Reproduced with permission from Steinberg L, Soong C, Safavi N, Daly A (2019) Improving your goals of care conversation. *Sinai Health System*. Available at: http://www.goalsofcaremodule.com (Accessed Sept 29, 2019).
37. **Scheunemann LP, Cunningham TV, Arnold RM** *et al.* (2015) How clinicians discuss critically ill patients' preferences and values with surrogates: an empirical analysis. *Crit Care Med*, **43**, 757–64.
38. **Visser M, Deliens L, Houttekier D** (2014) Physician-related barriers to communication and patient- and family-centred decision-making towards the end of life in intensive care: a systematic review. *Crit Care*, **18**(6), 604.
39. **Weiner JS, Roth J** (2006) Avoiding iatrogenic harm to patient and family while discussing goals of care near the end of life. *J Palliat Med*, **2**, 451–63.
40. **Feudtner C, Walter JK, Faerber JA** *et al.* (2015) Good-parent beliefs of parents of seriously ill children. *JAMA Pediatr*, **169**(1), 39–47.
41. **Rasmussen K, Raffin-Bouchal S, Redlich M, Simon J** (2018) Duty to defend: patient and family experiences of advance care planning conversations held prior to intensive care unit admission. *Can J Crit Care Nurs*, **29**(3), 19–25.
42. **Myers J, Cosby R, Gzik D** *et al.* (2018) Provider tools for advance care planning and goals of care discussions: a systematic review. *Am J Hosp Palliat Care*, **35**(8), 1123–32.
43. **Nesari M, Douglas M, Ghosh S** *et al.* (2019) A systematic review of economic evaluations of advance care planning: data limitations and ethical considerations. *BMJ Support Palliat Care*, **9**, A18.

Chapter 2

Opioids overview

Pippa Hawley

Attitude

To enable each learner to:

- Recognize that severe pain is a medical emergency.
- Understand that ability to prescribe opioids safely and effectively is a core competence for physicians.

Skills

To enable each learner to:

- Formulate a pharmacological pain management plan using the World Health Organization (WHO) pain ladder.
- Recognize different situations where one opioid is preferable to another.
- Be able to switch from one opioid to another, safely and effectively.

Knowledge

To enable each learner to:

- Describe the different types of opioid receptors.
- Describe the pharmacological properties of different opioid analgesics and their side-effects.
- Describe opioid-induced hyperalgesia and tolerance.

Case 2.1

C.C. is a 64-year-old lady with endometrial cancer and continuous lower abdominal pain which radiates to the low back. She asks you for something to help relieve her pain.

Question 1. How would you approach this request?

The most widely used approach to cancer pain was developed by the WHO. According to the WHO, there are 18.1 million new cancer cases in the world every year, and one in six deaths—about 9.6 million—are from cancer. Around 55% of cancer patients undergoing treatment will experience pain, and up to 70% with advanced cancer. Many more are cured from cancer but live with painful sequelae.

The WHO's pain relief ladder (see Figure 2.1) was designed to improve access to effective pain management for people with cancer, with all countries encouraged to have at least one agent at

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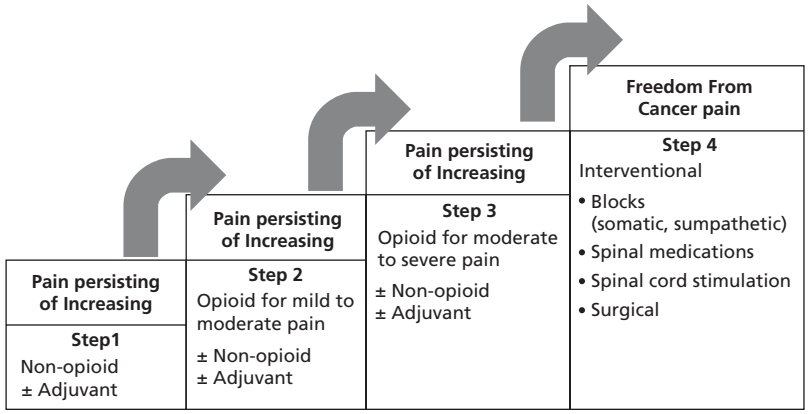


Fig. 2.1 The World Health Organization pain relief ladder.
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each of the three steps. It has subsequently been modified by experts in the field to include an additional Step 4 (Procedures, Lidocaine Infusions) for those with severe pain not responding to Step 3 agents.[1] The original 3-step ladder has been shown to be effective in about 85% of people when applied appropriately. In practicality, the success of the ladder is severely constrained in many places by lack of access to adequate drugs and by lack of knowledge of how to prescribe them. Non-opioids, such as acetaminophen or aspirin, are recommended for mild pain, and for moderate pain, it suggests 'stepping up' to a weak opioid, then up again to a 'strong opioid' if needed.

A Step 2, or 'weak', opioid is one that has a ceiling effect due to one of two characteristics. The first is because of a need for transformation to an active metabolite which is an enzymatic process that has limited capacity, such as for codeine or tramadol. The second is when a drug is co-formulated with another drug such as acetaminophen, which has a limit on the safe amount that can be consumed without risking toxicity. Oxycodone with acetaminophen (Percocet®) is an example of this type. Acetaminophen with codeine ± caffeine (e.g. Tylenol® #3) and tramadol with acetaminophen (Tramacet®) are Step 2 agents for both reasons.

In addition to its agonist effect on opioid receptors, tramadol has an additional ('adjuvant') serotonin–noradrenaline reuptake inhibitor (SNRI)-like mechanism of action which is thought to contribute to its analgesic effect. Tapentadol is a stronger Step 2 opioid with a similar SNRI-like adjuvant analgesic effect.

Many experienced clinicians believe that Step 2 of the ladder has little to no role in cancer pain, and go straight to a Step 3 opioid if a Step 1 analgesic is inadequate. The reasons for this include:

- Potential toxicity from unrecognized duplication of acetaminophen in over-the-counter combination preparations.
- Variable rates of activation between individuals which can cause an inadvertent overdose or inadequate effects, and unpredictable equianalgesic potency when switching to a Step 3 opioid.

Between 5 and 10% of Caucasians possess allelic variants of the *CYP2D6* gene that are associated with reduced metabolism of codeine to its active form morphine, but the prevalence of variants associated with increased metabolism varies more widely. The prevalence of *poor* metabolizers (i.e. do not benefit from codeine) is lower in Asian populations (≤1%) and highly variable in African populations (0–34%). The prevalence of *rapid* metabolizers (i.e. can get dangerously high

levels of morphine from codeine) can be as low as 1% in Asian populations and as high as 30% in some Africans. Similarly, there can be a 14-fold difference in bioavailability of tramadol between individuals, depending on their genetic metabolizer status.[2]

Step 3 opioids do not have a ceiling effect, with an incrementally greater analgesic effect derived as the dose increases. Some patients with increasing pain due to progressive disease continue to respond to increasing doses without side-effects, but many do develop toxicity when doses escalate, and it is helpful to have access to multiple opioids in order to be able to maximize effectiveness and minimize side-effects. Just as our endogenous opioid-like molecules have different effects, all opioids are not equal. Each opioid affects a different spectrum of opioid receptors, and different opioids have characteristics that make one or another more appropriate than others under certain circumstances. There is much genetic inter-individual variation in opioid responsiveness, as well as in opioid metabolism. Disease states can also alter metabolism, and different pain generators can vary in sensitivity to different opioids, particularly neuropathic pains.

There are three main types of opioid receptors: μ (mu), κ (kappa), and δ (delta), all of which have been shown to have multiple subtypes. A fourth type of receptor—opioid receptor-like (ORL)/nociceptin opioid (NOP)—has been identified, but this receptor is not affected by most opioid drugs and has more effects outside of the pain-sensing system. Opioid receptors exist throughout the nervous system where they are involved in pain perception and processing, but they are also present in peripheral organs, such as the heart, lungs, liver, and gastrointestinal (GI) and reproductive tracts, where they have a variety of other functions, including emotional regulation. Opioids have also been shown to suppress cancer cell growth and promote apoptosis in some leukaemias and to be cardioprotective in cardiac ischaemia and neuroprotective in stroke, amongst other effects.[3]

Non-cancer pain

Many medical conditions may produce pain that can be as severe and as distressing as cancer pain. While the WHO ladder was created specifically for cancer pain, the same general principles can be applied to other pain and the use of opioids for them.

Opioid side-effects

All opioids can cause side-effects, most commonly dry mouth, constipation, sedation, dizziness, and nausea. The occurrence of these side-effects varies from one person to another but rarely preclude their use altogether. Tolerance does not develop to constipation or pruritus, but nausea and sedation generally pass as the patient gets used to being on an opioid. If not resolved within a week, a trial of an alternative opioid may be helpful. Other rare side-effects of opioids include rashes, transient pulmonary oedema, hypotension, and bradycardia.

If dosed in excess of analgesic requirements, all opioids can cause respiratory depression. They can also increase airway resistance and decrease the patency of the upper airways. Opioids should therefore be used with great caution in patients with asthma who are ventilated or have sleep apnoea, especially if given concurrently with benzodiazepines or other sedative drugs.

Long-term use of opioids can also suppress gonadotrophins and result in hypogonadism. In the end-of-life context, this is not usually a major concern, but in long-term use, especially in non-cancer conditions, it can become a clinically relevant problem and hormone replacement therapy may be warranted.

Opioids

The Step 3 opioids commonly available for chronic cancer pain in Canada include:

- Morphine.
- Hydromorphone.
- Oxycodone.
- Fentanyl.
- Methadone.
- Buprenorphine (rarely used in cancer pain).
- Sufentanil (for severe incident pain only).
- Alfentanil (very rarely used).

Sufentanil is a lipophilic opioid that is more potent than fentanyl and can be given sublingually for rapid-onset analgesia with a short duration of action for incident pain such as for dressing changes or having bowel movements in the presence of painful anorectal conditions.

Alfentanil is an even stronger rapid-acting lipophilic opioid that is only used for very difficult situations of acute (incident) pain where very high doses are required.

Morphine

Morphine is the first-line opioid in Canada and has an agonist effect on a wide range of opioid receptors. It is the 'gold standard' opioid against which other opioids are compared. Morphine is available in oral immediate-release (tablets and solution), oral sustained-release (12-hour and 24-hour) capsules and tablets, suppositories, and injectable preparations. It is transformed in the liver to two main metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G is analgesic, but M3G is not, and M3G is thought to be the main source of adverse effects sometimes seen with morphine such as myoclonus and delirium. M6G and M3G are both cleared by the kidneys, so when renal function is impaired, the metabolites can accumulate, especially M3G. Repeated use of morphine is therefore best avoided in those with renal impairment.[4]

Morphine can be administered orally, rectally, or parenterally but, in high concentrations, is not very soluble and can crystallize out under the skin when administered subcutaneously in high doses. Morphine undergoes significant first-pass effect, and in those unused to oral morphine, it is about 50% bioavailable. Prolonged exposure to oral morphine, however, leads to induction of the metabolizing enzyme systems in the liver and gut wall, so bioavailability can drop to as low as 30% in some patients. When changing morphine administration from oral to parenteral, the duration of oral exposure should be taken into consideration when calculating an equivalent parenteral dose. This is not an exact science, as there are many other factors to be taken into consideration, and there is wide inter-individual variation. Equianalgesic tables (see Table 2.1) that are used to guide prescribers when switching from one route to another, and from one opioid to another, should be viewed very much as suggestions, rather than rules, and patients observed closely following a switch so that adjustments can be made promptly in the event of apparent under- or overdosing.

Table 2.1 Opioid equianalgesic chart from the National Pain Centre at McMaster University

Equivalence to oral morphine 30 mg	To convert TO oral morphine, multiply by	To convert FROM oral morphine, multiply by
Codeine 200 mg	0.15	6.67
Oxycodone 20 mg	1.5	0.667
Hydromorphone 6 mg	5	0.2

Adapted with permission from Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain, McMaster University. Available at http://nationalpaincentre.mcmaster.ca/opioid/cgop_b_app_b08.html.[8]

Hydromorphone

Hydromorphone is a semi-synthetic version of morphine and is approximately five times more potent than morphine. It is more soluble, so less likely to irritate the tissues when administered in high doses subcutaneously. Like morphine, hydromorphone is metabolized by the liver and the metabolites are cleared by the kidneys, but high doses can lead to accumulation of the glucuronide metabolite hydromorphone-3-glucuronide (H3G) which can cause seizures, amongst other adverse effects. Hydromorphone is available in oral immediate-release (tablets and solution) and oral sustained-release (12-hour and 24-hour) capsules and injectable preparations.

Oxycodone

Oxycodone is also a semi-synthetic version of morphine but is only about 1.5 times as potent as morphine. It is not available in Canada in injectable form, which leads to the added complication of patients needing to be switched to an alternate opioid, rather than just a route change when the oral route is lost, as often occurs at the end of life. Oxycodone absorption can be increased by high-fat meals, and its metabolism is more subject to inter-individual variation than that of morphine or hydromorphone. Clearance is slower in women than in men.

Oxycodone has mildly serotoninergic effects. Though it is more usually sedating, in some people, it can actually be energizing. This can be a helpful side-effect in fatigued patients, but some people experience agitation and aggression with oxycodone that they do not get with other opioids. Oxycodone is available in immediate-release tablets and in 12-hour time-release formulations.

The original sustained-release oxycodone product OxyContin® was made in a matrix formulation, the slow-release characteristics of which could be overcome easily by crushing and snorting (nasal inhalation) or dissolving in water for injection. Oxycodone itself also seems to have a higher propensity for development of opioid use disorder than other commonly available opioids. The manufacturer has now substituted an abuse-deterrent formulation OxyNeo®, which is slightly sticky and, when crushed, forms a gel that is difficult to administer nasally or by injection. OxyNeo® tablets can be hard for some patients to swallow, and the preparation is expensive. Generic preparations of OxyContin® are now available but should be used with caution in those with risk factors for substance use disorders.

Fentanyl

Fentanyl is a synthetic opioid which is more lipophilic than other opioids, and is well absorbed transdermally. Taken orally, it undergoes extensive first-pass metabolism, is not known to have any active metabolites, and is cleared by the liver, making it a preferred opioid in the presence of renal failure. Despite having quite good absorption transmucosally, it is less potent than sufentanil and rarely used for incident pain via this route because of the volume that would be required. Fentanyl has a serotoninergic effect, in addition to its opioid receptor agonism, and can precipitate serotonin syndrome if given concurrently with other drugs that are serotoninergic such as selective serotonin reuptake inhibitor (SSRI) or SNRI antidepressants (see Chapter X for more information on serotonin syndrome).

Fentanyl patches allow the drug to migrate through the skin into subcutaneous fat, from where it is distributed around the body via blood. It takes 12–24 hours for the blood level of fentanyl to plateau following the first patch application, and each patch is expected to last for 3 days. This needs to be taken into consideration when switching to fentanyl from other opioids. The subcutaneous depot of fentanyl takes time to be absorbed, by which time the next patch is taking effect, resulting in a fairly steady blood level with repeated patch applications. Fentanyl patches are therefore inappropriate for use in acute pain or for incident pain syndromes. They are also

inappropriate in opioid-naïve patients, as even the smallest strength patch (12mcg/hr) contains a significant amount of opioid.

Fentanyl patches were originally produced in a gel sandwich method, with a rate-limiting semi-permeable membrane separating the fentanyl-containing gel from the skin. Reports of accidental rupture of the seal allowing the gel to escape, sometimes with fatal consequences, led to having the drug embedded in an adhesive matrix that cannot leak out, even if the patch is cut. All brands of fentanyl patch available in Canada are now of the matrix design, and though cutting of patches to facilitate fine-tuning of doses is not recommended, there are occasions when it can be necessary. If a dose smaller than a whole patch (or in between strengths available) is used, it is important to carefully document the dosing, and it may need covering with an additional clear adhesive patch to ensure it does not come off unexpectedly.[5]

Though still constipating, transdermal fentanyl is generally less constipating than other opioids, which makes it a useful option where there is already severe constipation, despite a good bowel protocol, or a risk of bowel obstruction. Fentanyl affects a somewhat different range of opioid receptors than other opioids and some patients seem to derive very little benefit from it, even at high doses, which can make its potency, as compared with other opioids, difficult to predict. Absorption of the drug can also vary not just between individuals, but also depending on the characteristics of the skin on different parts of the body and the amount of subcutaneous fat. Application is recommended to be on the upper body ('above the heart'), on a non-hairy area that has no scars, moles, or open sores and has not previously been irradiated, preferably staying within areas of consistent skin thickness, such as alternating between left and right subclavian areas or the deltoid area of the shoulders.

Only on rare occasions do patients need a q48-hour patch change schedule. In patients with severe cachexia or who are approaching end of life and shutting down their peripheral circulation, transdermal fentanyl may start to lose effectiveness and a parenteral route may be required.

Methadone

Methadone is a synthetic opioid that has a special and very important role in pain management and is discussed in detail in Chapter 31.

Buprenorphine

Buprenorphine is a recent addition to the options for pain management in palliative care in Canada, though it has been available in Europe for many years. As yet, in Canada, it is rarely used for pain in advanced illness such as cancer. It is available in Canada as a transdermal patch and, in pure form, orally in tablets which are restricted in Canada to opioid substitution therapy during pregnancy. Buprenorphine has complex effects on opioid receptors, being an agonist of the μ and δ receptors, and simultaneously an antagonist of the κ kappa receptors. When added to the therapy of a patient already on an opioid, it could theoretically precipitate a partial withdrawal syndrome. Buprenorphine seems clinically to have a ceiling above which incremental dose increases do not result in greater analgesia, like a Step 2 opioid. The widespread use of buprenorphine in a combination preparation with naloxone (Suboxone®) for opioid substitution therapy can lead to confusion amongst family and caregivers about the goal of therapy. Suboxone® can, however, have a niche for analgesia in the rare individuals who have adverse effects from all other opioids.

Adjuvant analgesics

At all levels of the WHO cancer pain ladder it is appropriate to consider the co-administration of non-opioid medications, in order to improve analgesia and minimize the need for opioids. These

drugs are collectively termed 'adjuvant analgesics' and are discussed in Chapters X and X in relation to specific subtypes of pain.

Question 2. What might be the best initial choice of analgesic for C.C.?

C.C.'s pain is coming from the enlarging pelvic/abdominal mass, and the pain is visceral in nature. Visceral pain is generally quite opioid-sensitive but may also respond to anti-inflammatory drugs.

There are no features of neuropathic pain and C.C. does not have renal impairment. She has no history of reflux, gastritis, or GI bleeds. She is not at increased risk of bleeding. It would therefore be appropriate to initiate trial of a non-steroidal anti-inflammatory drug (NSAID), such as naproxen, which could be administered along with acetaminophen if both are helpful. You ask her if she has tried these already, as many patients do so before seeking medical attention for pain, since these drugs are widely available without prescription.

Case 2.1 (continued)

C.C. tells you she has been taking ibuprofen or naproxen, along with up to ten tablets a day of extra-strength acetaminophen for over 2 weeks, and they do help, but she still has significant pain.

Question 3. How would you start C.C. on an opioid?

As C.C. is likely to have pain from her cancer for the foreseeable future, and dose increases are likely as her disease progresses, it would be very reasonable to bypass Step 2 of the ladder and start a low dose of a Step 3 opioid such as morphine 10 mg of 12-hour sustained-release every 12 hours. It would alternatively be perfectly reasonable to start 5 mg immediate-release tablets and assess the effect over the next day or two, switching to long-acting once the dose required for comfort is established. Whichever approach is taken for regular dosing, a short-acting preparation should also be prescribed on an additional as-needed basis.

When starting any opioid, you should always prescribe a bowel protocol, for example regular sennosides, with doses titrated to effect. In addition, you should provide a prescription for some metoclopramide to be filled if needed, as about a third of patients starting opioid therapy will experience some transient nausea for the first week or so.

Case 2.1 (continued)

Two days later, C.C. tells you she is much more comfortable and has only needed to take one of the breakthrough tablets. She has felt a little nauseated a couple of times but has not vomited and does not feel the need to take an antiemetic at this time. Her bowels are moving normally with two sennosides at bedtime.

Question 4. What are some potential situations which might require you to switch C.C. to a different opioid?

If C.C. develops renal impairment (e.g. from chemotherapy or ureteric obstruction) or constipation becomes an issue despite her bowel protocol, a switch to fentanyl or methadone would be

a good choice as they do not have active renally cleared metabolites. Hydromorphone can be a good alternative at low to moderate doses, but in high doses, norhydromorphone (an active metabolite) can accumulate and cause toxicity. If she develops neuropathic pain from lumbosacral plexus invasion or chemotherapy-induced peripheral neuropathy, a switch to methadone may be helpful, plus adjuvant analgesics for neuropathic pain should be considered. If she becomes very fatigued or experiences sedation, myoclonus, pruritus (itching), or other side-effects from morphine, a switch to a different opioid may be helpful. Delirium is common in advanced cancer and usually multifactorial, but if opioid therapy is thought to be a/the cause, an opioid switch will be necessary. Fentanyl and methadone are less likely to cause delirium than morphine, hydromorphone, and oxycodone, presumably because of their lack of active metabolites.

There has been little clinical research comparing opioids, and the best approach is one of trial and error until the opioid with the least side-effects and the best effect is determined. Financial and practical issues with drug availability will also need to be taken into consideration. Coverage varies from one province/territory to another and prescribers need to be familiar with the regulations that apply in their region.

Tolerance and hyperalgesia

Hyperalgesia and tolerance are indications for either a switch to a different opioid or reduction/cessation of opioid therapy (if appropriate, i.e. the original pain generator that led to opioid therapy is thought to have resolved), and/or consideration of non-opioid-based analgesia if the pain generator is still present.

Hyperalgesia is lowering of the pain threshold. The severity of discomfort caused by a noxious stimulus increases without the intensity of the stimulus changing. Localized hyperalgesia is easy to detect, e.g. around a small burn. The mechanism for this is different to that of generalized hyperalgesia and involves local spinal cord reflexes. Generalized hyperalgesia occurs through central mechanisms and patients with this feel pain in parts of the body remote to any noxious stimulus. They may flinch on minor physical contact, e.g. when having their blood pressure taken, on application of a stethoscope, or on palpation of the abdomen. Even hair brushing can cause discomfort. Though more common with high-dose opioid therapy, generalized hyperalgesia can be seen at any opioid dose, particularly when there is potential for accumulation of metabolites such as in the elderly or those with impaired renal function. Opioid-induced hyperalgesia arises through different mechanisms than those involved with primary hyperalgesic conditions, e.g. fibromyalgia, which is a central pain sensitization syndrome thought to arise from dysfunction of the endocannabinoid system.[6]

Tolerance should be suspected when doses of opioid have to be gradually increased in order to continue to achieve the same degree of analgesia, in the absence of (or insufficient degree of) increasing intensity of noxious stimulus. Patients may have tolerance without hyperalgesia, and vice versa, but they often coexist.

Switching opioids

There are many opioid equianalgesic charts and online calculators, and it is important to use one that is up-to-date. Most are based on morphine equivalent dosing (MEDD). A recent Health Canada guideline gives morphine oral to parenteral a conversion ratio of 3:1, instead of the more traditionally understood 2:1 ratio, bearing in mind the issue of induction of the first-pass effect and erring on the side of caution.[7] The pharmacology behind this should be clearly understood to avoid potential for under-dosing of parenteral morphine when patients have not been on oral morphine long enough to induce the metabolizing enzyme pathway. Similarly, when using a chart to convert from one opioid to another, especially with the added complexity of a route change,

Table 2.2 Equianalgesic doses of oral morphine and fentanyl

Oral morphine total daily dose (mg)	Fentanyl patch strength (mcg/hour)
45–59	12
60–134	25
135–179	37
180–224	50
225–269	62
270–314	75
315–359	87
360–404	100

there is inevitably going to be a margin of error for each calculation and a two-step conversion (such as converting from codeine to morphine, then to parenteral hydromorphone for someone who is not able to swallow) will magnify the error of the first calculation.

Note that not all patch strengths are commercially available but can be made by application of multiple patches. For higher doses, the equianalgesic dose can be extrapolated from the chart, as the conversion ratio does not appear to change in a dose-dependent fashion.[8]

Though tolerance develops over time, because the different opioids have slightly different opioid receptor agonist effects, the tolerance developed to the first opioid may not carry over fully to the second opioid, a concept called non-cross-tolerance. For this reason, it has become customary to reduce the estimated equivalent dose of the second opioid by about 25% when switching, monitoring the patient closely until the switch is completed to ensure adequate doses are provided. While appropriate for those experiencing opioid toxicity, this can lead to under-dosing for those experiencing inadequate analgesia, and adequate breakthrough should be provided until dose requirements are established.

References

1. **Vargas-Schaffer G** (2010) Is the WHO analgesic ladder still valid? *Can Fam Physician*, **56**(6), 514–17.
2. **Dean L** (2012) Codeine therapy and *CYP2D6* genotype. *Medical Genetics Summaries*, updated 2017. https://www.ncbi.nlm.nih.gov/books/NBK100662/
3. **Feng Y**, **He X**, **Yang Y**, **Chau D**, **Lazarus L**, **Xia Y** (2012) Current research on opioid receptor function. *Curr Drug Targets*, **13**(2), 230–46. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3371376/
4. **Smith H** (2009) Opioid metabolism. *Mayo Clin Proc*, **84**(7), 613–24. doi: 10.1016/S0025-6196(11)60750-7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2704133/
5. **Cheng P**, **Hawley P** (2017) Experiences with cutting matrix fentanyl patches as a method of dose titration in cancer patients. *J Palliat Med*, **20**(12), 1311–12. doi: 10.1089/jpm.2017.0368
6. **Russo EB** (2016) Clinical endocannabinoid deficiency reconsidered: current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. *Cannabis Cannaboid Res*, **1**(1), 154–65. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5576607/
7. **Health Canada** (2010) *Fentanyl transdermal systems: new changes to the dose conversion guidelines—for health care professionals*. http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2010/14603a-eng.php
8. **Michael G DeGroote National Pain Centre**. *Canadian guideline for safe and effective use of opioids for chronic non-cancer pain*. http://nationalpaincentre.mcmaster.ca/opioid/cgop_b_app_b08.html

Chapter 3

Somatic pain

Megan Sellick, Yoko Tarumi, and Sharon M. Watanabe

Attitude

To enable each learner to:

- Reflect on the importance of somatic pain, particularly cancer-induced bone pain (CIBP), for function and quality of life.
- Realize the clinical urgency of diagnosing and preventing pathologic fractures.
- Consider appropriate patients for referral for radiotherapy or orthopaedic consultation.

Skills

To enable each learner to:

- Diagnose CIBP clinically.

Knowledge

To enable each learner to:

- Describe the pathophysiology and epidemiology of CIBP.
- Choose appropriate diagnostic modalities for bone metastases.
- Apply pharmacological and non-pharmacological strategies for CIBP.

Case 3.1

T.H. is a 67-year-old farmer, diagnosed 2 years ago with localized prostate adenocarcinoma. Staging imaging was negative for metastasis. He received external beam radiotherapy to the prostate and margins, followed by androgen deprivation therapy. The most recent prostate-specific antigen (PSA) is 105 ng/ml.

He sees his family doctor, reporting generalized aches and a 1-day history of right groin pain, for which acetaminophen 500 mg every 6 hours is ineffective. At rest, the pain is mild (2/10), but with walking, it is 7/10. Walking also triggers achy pain in his right thigh. He denies radiation of pain to the knee, sensory changes, or loss of power.

Question 1. What are the clinical features of somatic pain?

Somatic pain is a subtype of nociceptive pain arising from bone or soft tissue. In patients with cancer, pain related to bone metastases is the most commonly encountered somatic pain syndrome.[1]

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The skeleton is one of the most frequent sites of metastases. Breast and prostate cancers are most often responsible for malignant bone disease, occurring in 70% of patients with these diagnoses.[2] Thyroid, lung, and kidney cancers also frequently metastasize to bone, while multiple myeloma involves bone diffusely. Most patients with bone metastases will develop 'skeletal-related events' (SREs) such as bone pain, pathologic fractures, hypercalcaemia, and spinal cord compression. Although pain is the most common presenting symptom, 30–50% of patients with bone involvement are asymptomatic and lesions are found during staging studies for primary tumours.[3]

CIBP usually manifests as continuous pain, with episodes of aggravation of pain, known as breakthrough pain (BTP). While international consensus is lacking, BTP is considered a transient exacerbation of pain, occurring spontaneously or related to a trigger, on a background of stable and adequately controlled pain.[4] Patients with CIBP can develop severe pain with normally non-painful activities such as coughing, turning in bed, gentle touch, or gentle limb movements. CIBP is often well localized and aching or gnawing in quality.[5] It is often provoked or aggravated by palpation of the affected area. Bone metastases and associated pain have ominous consequences for prognosis of both quality and length of life.[6,7]

Question 2. What is the pathophysiology of somatic pain?

The pathophysiology of somatic pain has been best described for CIBP and includes several factors.[8] CIBP may arise from compromise of mechanical stability of bone. Osteoclasts and osteoblasts are responsible for bone resorption and formation, respectively. Osteoblasts and marrow stromal cells normally express the receptor activator of nuclear factor-kappa B ligand (RANKL). RANKL binds to the RANK receptor on osteoclast precursors, promoting maturation and proliferation. Excessive bone resorption is prevented by the decoy receptor osteoprotegerin, produced by osteoblasts, that binds to RANKL, preventing interaction with the RANK receptor. Control of this system is lost when cancer and immune cells invade the bone micro-environment and secrete RANKL, leading to excessive osteolysis.

CIBP may also arise from damage to, and deformation of, nerves in bone. Bone has rich sensory and sympathetic fibre innervations, which can induce pain when stimulated. Cancer cells cause disorganized nerve sprouting and neuroma formation, leading to induction of pain by normally non-painful stimulation of sympathetic nerves and episodes of spontaneous pain. Nerve growth factor (NGF) has been implicated in this process. Moreover, NGF directly stimulates nociceptors and lowers neuron activation thresholds.

Additionally, tumour and immune cells secrete prostaglandins and other inflammatory cytokines, which can sensitize the peripheral nerves to pain stimuli directly and by creating a more acidic environment.

A further factor in CIBP is central nervous system sensitization. At the spinal level, extensive neurochemical and neurobiological reorganization occurs, including expression of the pro-hyperalgesic peptide dynorphin and proliferation of astrocytes in the dorsal horn. Also, the proportion of wide-dynamic range neurons, which are responsible for hyperexcitability to painful stimuli, increases.

Case 3.1 (continued)

When examined, T.H. is not cachectic and has mild gynaecomastia. He has a normal stance, but an abnormal gait due to painful ambulation. Passive range of motion in the right hip is normal. He has tenderness with palpation of the right ischial tuberosity.

Question 3. What tests support the diagnosis of painful bone metastases?

Bone consists of 85% dense cortical bone composed of minerals and 15% porous and spongy trabecular bone composed of collagen and mineral content, which encompasses the marrow component. Most of the red marrow is located in the axial skeleton, while fat marrow is located in appendicular bones.

On plain radiographs, bone metastases may appear as areas of absent density or absent trabecular structure, representing osteolytic lesions. Osteoblastic lesions may appear as increased density and sclerotic lesions or rims. Plain radiographs can confirm symptomatic or suspicious lesions on bone scintigraphy and are used to assess patients at high risk of pathologic fractures. However, because 30–75% of normal bone mineral content must be lost before osteolytic vertebral lesions become apparent on X-rays, metastatic lesions may not be apparent for several months.[9] The diagnostic sensitivity for X-ray is approximately 44–50%, which is substantially lower than bone scans for detecting bone metastases.[10] However, plain radiographs are useful as a primary investigation and for purely lytic disease (e.g. multiple myeloma) where bone scans are commonly falsely negative.

Diagnostic sensitivity of bone scans ranges from 62 to 100%, with a specificity of 78–100%.[10] However, they lack specificity as they may show uptake in non-cancer conditions (osteoarthritis, infection, trauma, Paget's disease), because they commonly show abnormal osteoblastic activity. Additionally, bone scans may be negative in purely lytic, or rapidly progressive, disease because there is little chance for new bone formation. Computed tomography (CT) with bone windows or magnetic resonance imaging (MRI) can provide detailed information of the bone and marrow, with MRI having better contrast resolution for visualizing soft tissue and the spinal cord. The diagnostic sensitivity for bone metastases with CT and MRI ranges from 71 to 100% and 82 to 100% (with a specificity of 73–100% for MRI), respectively.[10] Positron emission tomography (PET) may have a role in early detection of soft tissue or bone metastases. Although high in sensitivity and specificity, its significance can be limited by higher cost and relatively limited availability.

Case 3.1 (continued)

Plain radiographs of T.H.'s lumbosacral spine and pelvis show no significant abnormality, except superolateral joint space narrowing, osteophytes, and loss of bone mineral density. A bone scan shows marked uptake throughout the axial and proximal appendicular skeleton.

Question 4. What is the initial pharmacological approach to managing CIBP?

The principles of pharmacological management for CIBP follow the World Health Organization (WHO) guidelines[11] whereby the goal of treatment is to reduce pain to a level that creates a quality of life acceptable to the patient. When adequate analgesia is no longer achieved by non-opioid analgesics alone, opioids remain the main pharmacological approach despite the recent review noting side-effects in 1–2/10 people.[12]

BTP in cancer, as discussed earlier, is significantly associated with bone metastasis, worse pain management outcome, interference with activities of daily living, and decreased quality of life.[4] The Alberta Breakthrough Pain Assessment Tool is one of few validated assessment tools that incorporates important aspects of BTP (frequency, severity, and location) and aims to distinguish

BTP from uncontrolled pain.[13] BTP should be treated with rescue analgesia that is 50–100% of the regular 4-hourly opioid dose, in immediate-release formulation.[11] However, the challenge is that BTP generally has a rapid onset and short duration, while immediate-release opioid formulations take 30–40 minutes to achieve meaningful pain relief and last 3–6 hours. In contrast, transmucosal fentanyl citrate may provide rapid-onset pain relief that better matches the time course of BTP as it is a lipophilic molecule, which is directly absorbed across the mucosa and rapidly distributed to tissues and plasma.[14] However, published studies of transmucosal fentanyl in BTP in cancer have methodological issues and potential bias that limit the ability to identify its clinical superiority over other immediate-release opioids.[14] The cost, tolerability, and safety of transmucosal fentanyl also prohibit its use in multiple clinical settings.[11,14] The WHO and National Institute for Health and Care Excellence (NICE) guidelines recommend an immediate-release opioid, such as morphine, as the first-line treatment for BTP.[11,15]

Question 5. What non-opioid pharmacological agents may be useful for CIBP?

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the enzyme cyclo-oxygenase (COX). The COX-1 isoform is found in platelets, the gastrointestinal tract, the kidneys, and most other human tissues. COX-2 is found predominantly in the kidneys and central nervous system, and is induced in peripheral tissues by noxious stimuli that cause inflammation and pain. In addition to peripheral effects, NSAIDs exert a central action at the brain or spinal cord level. NSAIDs are effective in cancer pain,[16] although there is no evidence they are more effective in CIBP, compared to other pain syndromes. NSAIDs can have adverse effects, including renal failure and gastrointestinal ulceration. The risk of gastrointestinal toxicity is higher with increased age, previous peptic ulcer disease, comorbidities, use of multiple NSAIDs [including acetylsalicylic acid (ASA)], and use in combination with corticosteroids. Some clinicians prescribe a gastroprotective agent, though there is no strong evidence to promote this as routine practice.

Corticosteroids are frequently prescribed to manage multiple symptoms. One small randomized controlled trial of methylprednisolone versus placebo in patients with advanced cancer on opioids did not demonstrate an analgesic effect for pain of any mechanism, including CIBP.[17] A multicentre, randomized controlled trial in patients receiving a single fraction of palliative radiotherapy to a painful bone metastasis showed that dexamethasone reduced the incidence of pain flare.[18] Side-effects occur particularly with prolonged use (e.g. thrush, osteoporosis, myopathy). Therefore, it is preferable to use corticosteroids on a short-term basis, while other analgesic interventions take effect.

Bisphosphonates are synthetic analogues of pyrophosphate which bind to bone matrix and cause osteoclast apoptosis, thereby reducing bone resorption. Regular administration of bisphosphonates has been shown to reduce SREs in patients with breast cancer metastatic to bone and multiple myeloma;[19,20] evidence of benefit in other types of tumour metastatic to bone is evolving. A systematic review concluded that bisphosphonates may delay onset of bone pain, but there is insufficient evidence to recommend bisphosphonates for immediate analgesic effect; generally, the analgesic benefits have only been seen in specific cancer diagnoses (namely prostate and breast cancers) and after long-term use.[21] Available bisphosphonates include clodronate, pamidronate, zoledronic acid, and ibandronate (availability varies among countries). The parenteral route is preferred due to superior bioavailability, avoidance of gastrointestinal distress, and, probably, better analgesic effect. Clodronate is unique in its ability to be given subcutaneously, which may be advantageous in the palliative care setting.[22] Bisphosphonates may harm renal function, an uncommon event if given according to recommended dosing. Renal impairment is

usually reversible; nonetheless, monitoring renal function and hydration are essential. Another potential complication is osteonecrosis of the jaw; pre-treatment dental assessment and intervention, and monitoring of dental health during treatment, are recommended.[23]

Denosumab is a human monoclonal antibody with high affinity and specificity for RANKL. By neutralizing RANKL, denosumab inhibits osteoclast formation, function, and survival, thereby suppressing bone resorption. Studies in breast, prostate, and other solid tumours have demonstrated delayed time to first SREs, compared to zoledronic acid, pamidronate, and placebo,[24] but insufficient information exists on its effects on pain.[21] It is significantly more costly than bisphosphonates.

Calcitonin is a hormone that inhibits osteoclastic bone resorption. In injectable form, it is sometimes used in the treatment of hypercalcaemia of malignancy. A systematic review found only two small clinical trials evaluating calcitonin in the treatment of CIBP, concluding that available evidence does not support its use for this indication.[25]

Pregabalin is an anticonvulsant used for adjuvant treatment of neuropathic pain.[26] One multicentre, randomized controlled trial compared pregabalin to placebo in patients with CIBP receiving palliative radiotherapy. No differences in analgesic outcomes were seen between the two groups, although it is possible that effects of radiotherapy masked drug effects.[27]

Question 6. What non-pharmacological approaches may be considered?

Modification of the patient's living environment with equipment (walkers, wheelchairs, and grip bars), in addition to non-weight-bearing techniques, can help reduce pain. A recent systematic review of occupational therapy and adult cancer rehabilitation highlighted the potential underutilization of rehabilitation in cancer care, compared to other medical conditions such as heart disease or stroke. There is strong evidence that exercise is safe and beneficial for the majority of cancer types, regardless of prognosis and age, though evidence was limited to specific symptom-related CIBP and BTP.[28] A randomized trial of physical therapy during radiotherapy in patients with vertebral metastasis demonstrated improvement in biochemical markers of bone turnover. Pain intensity and quality of life were not outcome measures.[29]

Case 3.1 (continued)

T.H. is prescribed morphine immediate-release 5 mg orally (po) every 4 hours (q4h) around the clock and 2.5 mg po every 1 hour (q1h) as needed (prn), with a laxative and an antiemetic. Acetaminophen is stopped (no benefit) and he is referred to physiotherapy for walking aids. One week later, he returns for reassessment and requires an increased dose of morphine for pain control.

Question 7. When should referral for radiotherapy be considered?

External beam radiotherapy is a standard approach to management of CIBP that cannot be adequately controlled with analgesics. A systematic review showed that over 60% of patients can expect at least partial pain relief, and just over 20% can expect complete pain relief.[30] There is no difference in pain relief or adverse effects between single and multiple fractions. Patients receiving single-fraction radiotherapy may have a higher rate of re-treatment. However, single-fraction radiotherapy is less burdensome for patients and less costly for the healthcare system.

Case 3.1 (continued)

T.H. is referred to the cancer centre to discuss options for further therapy. He agrees to palliative radiotherapy to his right pelvis and femur, and to consider chemotherapy thereafter.

Question 8. What is the role of radiopharmaceutical therapy?

Radiopharmaceuticals are radioactive agents, administered intravenously, that localize to metastatic bone sites and deliver focal radiation. A systematic review including randomized controlled trials of strontium-89, samarium-153, rhenium-186, rhenium-188, and phosphorus-32 demonstrated that radiopharmaceuticals are associated with pain relief (number needed to treat = 5 for complete relief, and 4 for complete plus partial relief).[31] Main adverse effects are thrombocytopenia and neutropenia. Use of radiopharmaceuticals may best be considered for patients with multiple painful bone metastases where conventional analgesic regimens are unsatisfactory and local field radiotherapy is not appropriate. Patient selection for radiopharmaceutical therapy should consider marrow function, performance status, recent use of other marrow suppression agents, suitability for alternate interventions, and anticipated life expectancy of more than several months (onset of analgesia is typically measured in months).

Question 9. When should orthopaedic interventions be considered?

Consideration of orthopaedic interventions, including percutaneous vertebral augmentation, in patients with CIBP requires an individualized approach. Commonly, these interventions are used in the setting of pain due to actual, or impending, pathologic fractures. Mirel's scoring system is a validated tool combining clinical and radiographic factors (associated pain, location, size, osteoblastic versus osteolytic lesions) to assess fracture risk in metastatic bone disease. This is necessary because prophylactic treatment of impending fractures (versus established fractures) can lead to faster recovery.[32] While Mirel's scoring system has been criticized for its relatively low specificity, it is reproducible and applicable and remains the gold standard.[33]

A prospective study exploring surgical intervention for long bone metastasis found that while quality of life indicators did not improve, pain and functional scores did improve post-operatively, even a year after surgery, with no significant difference between those who received intervention for impending or pathologic fracture. Complications occurred at a rate of 35% and included wound infection, venous thromboembolism, and hardware failure. However, only one-quarter of patients completed 1-year follow-up (for various reasons), limiting conclusions.[34] Similarly, systematic reviews report that surgery can improve patient outcomes, but the way data are collected makes it difficult to draw conclusions across studies.[35,36] Decreased functional status and comorbidities can prolong recovery and increase post-operative complications, mandating an individualized approach. For some patients with pathologic fractures, when survival is less than short months, the benefits of pain control and quality of life may outweigh the risk of post-operative complications.

Percutaneous vertebral augmentation (vertebroplasty, balloon kyphoplasty) stabilizes vertebral bones compromised by metastatic bone disease, with the aim of improving pain control. These interventions too must be carefully considered, with complications and potential benefits being weighed for patients.[37]

Future research

Future studies should investigate efficacy, safety, and pharmaco-economics with standard trial protocols, including the assessment and measurement of pain outcomes, to improve opportunities for meta-analysis. Additionally, comparisons should be made against placebo and other analgesics.

Other agents are being studied for their role in the management of refractory somatic pain, including lidocaine and dexmedetomidine, in the palliative care population.[38]

Tanezumab is a humanized monoclonal antibody with high selectivity and specificity for NGF, inhibiting NGF binding to tropomyosin receptor kinase A and p75. A proof-of-concept trial evaluating efficacy and safety of tanezumab in patients with CIBP taking opioids suggested potential sustained analgesia.[39]

Evidence-based protocols for opioid cessation should be evaluated for patients no longer requiring opioids for CIBP. Furthermore, the impact on bone health with long-term opioid use related to hypogonadotropic hypogonadism is largely unexplored.

References

1. **Caraceni A, Portenoy RK** (1999) An international survey of cancer pain characteristics and syndrome. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain*, **82**(3), 263–74.
2. **Coleman RE** (2006) Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res*, **12**(20 suppl), 6243s–9s.
3. **Galasko CS** (1995) Diagnosis of skeletal metastases and assessment of response to treatment. *Clin Orthop*, **312**, 64–75.
4. **Hjermstad MJ, Kaasa S, Caraceni A** *et al* (2016) Characteristics of breakthrough cancer pain and its influence on quality of life in an international cohort of patients with cancer. *BMJ Support Palliat Care*, **6**, 344–52.
5. **Laird BJA**, **Walley J, Murray GD** *et al.* (2011) Characterization of cancer-induced bone pain: an exploratory study. *Support Care Cancer*, **19**, 1393–401.
6. **Norgaard M, Jensen AO, Jacobsen JB** *et al.* (2010) Skeletal related events, bone metastasis and survival in Denmark (1999 to 2007). *J Urol*, **184**(1), 162–7.
7. **Brown JE, Cook RJ, Lipton A** *et al.* (2010) Prognostic factors for skeletal complications from metastatic bone disease in breast cancer. *Breast Cancer Res Treat*, **123**(3), 767–79.
8. **Falk S, Dickenson AH** (2014) Pain and nociception: mechanisms of cancer-induced bone pain. *J Clin Oncol*, **32**(16), 1647–54.
9. **Vinholes J, Coleman R, Eastell R** (1996) Effects of bone metastases on bone metabolism: implications for diagnosis, imaging and assessment of response to cancer treatment. *Cancer Treat Res*, **22**(4), 289–331.
10. **Hamaoka T, Madewell JE, Podoloff DA** *et al.* (2004) Bone imaging in metastatic breast cancer. *J Clin Oncol*, **22**(14), 2942–53.
11. **World Health Organization** (2018) *WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents.* World Health Organization, Geneva.
12. **Wiffen PJ, Wee B, Derry S** *et al.* (2017) Opioids for cancer pain: an overview of Cochrane reviews. *Cochrane Database Syst Rev*, **7**, CD012592.
13. **Hagen NA, Stiles C, Nekolaichuk C** *et al.* (2008) The Alberta Breakthrough Pain Assessment Tool for cancer patients: a validation study using a Delphi process and patient think-aloud interviews. *J Pain Symptom Manage*, **35**, 136–52.
14. **Twycross R, Prommer EE, Mihalyo M** *et al.* (2012) Fentanyl (transmucosal). *J Pain Symptom Manage*, **44**(1), 131–49.

15. **National Institute for Health and Care Excellence** (2012) *Palliative care for adults: strong opioids for pain relief.* https://www.nice.org.uk/guidance/cg140/chapter/1-Recommendations#first-line-treatment-for-breakthrough-pain-in-patients-who-can-take-oral-opioids
16. **Nabal M, Librada S, Redondo MJ** *et al.* (2012) The role of paracetamol and nonsteroidal anti-inflammatory drugs in addition to WHO Step III opioids in the control of pain in advanced cancer. A systematic review of the literature. *Palliat Med*, **26**(4), 305–12.
17. **Paulsen O, Klepstad P, Rosland JH** *et al.* (2014) Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. *J Clin Oncol*, **32**(29), 3221–8.
18. **Chow E, Meyer RM, Ding K** *et al.* (2015) Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases: a double-blind, randomised placebo-controlled, phase 3 trial. *Lancet Oncol*, **16**(15), 1463–72.
19. **O'Carrigan B, Wong MHF, Willson ML** *et al.* (2017) Bisphosphonates and other bone agents for breast cancer. *Cochrane Database Syst Rev*, **10**, CD003474.
20. **Mhaskar R, Kumar A, Miladinovic B** *et al.* (2017) Bisphosphonates in multiple myeloma: an updated network meta-analysis. *Cochrane Database Syst Rev*, **12**, CD003188.
21. **Porta-Sales J, Garzon-Rodriguez C, Llorens-Torrome S** *et al.* (2017) Evidence on the analgesic role of bisphosphonates and denosumab in the treatment of pain due to bone metastases: A systematic review within the European Association for Palliative Care guidelines project. *Palliat Med*, **31**(1), 5–25.
22. **Walker P, Watanabe S, Lawlor P** *et al.* (1997) Subcutaneous clodronate: a study examining efficacy in hypercalcemia of malignancy and local toxicity. *Ann Oncol*, **8**(9), 915–16.
23. **Coleman RE** (2008) Risks and benefits of bisphosphonates. *Br J Cancer*, **98**(11), 1736–40.
24. **Ford JA, Jones R, Elders A** *et al.* (2013) Denosumab for treatment of bone metastases secondary to solid tumours: systematic review and network meta-analysis. *Eur J Cancer*, **49**(2), 416–30.
25. **Martinez-Zapata MJ, Roqué i Figuls M, Alonso-Coello P** *et al.* (2006) Calcitonin for metastatic bone pain. *Cochrane Database Syst Rev*, **3**, CD003223.
26. **Finnerup NB, Attal N, Haroutounian S** *et al.* (2015). Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*, **14**(2), 162–73.
27. **Fallon M, Hoskin PJ, Colvin LA** *et al.* (2016) Randomized double-blind trial of pregabalin versus placebo in conjunction with palliative radiotherapy for cancer-induced bone pain. *J Clin Oncol*, **34**(6), 550–6.
28. **Hunter EG, Gibson, RW, Arbesman M** *et al.* (2017) Systematic review of occupational therapy and adult cancer rehabilitation: part 1. Impact of physical activity and symptom management interventions. *Am J Occup Ther*, **71**(2), 7102100030p1-7102100030p11.
29. **Rief H, Omlor G, Akbar M** *et al.* (2016) Biochemical markers of bone turnover in patients with spinal metastases after resistance training under radiotherapy—randomized trial. *BMC Cancer*, **16**, 231.
30. **Rich SE, Chow R, Raman S** *et al.* (2018) Update of the systematic review of palliative radiation therapy fractionation for bone metastases. *Radiother Oncol*, **126**(3), 547–57.
31. **Roqué i Figuls M, Martinez-Zapata MJ, Scott-Brown M** *et al.* (2011) Radioisotopes for metastatic bone pain. *Cochrane Database Syst Rev*, **7**, CD003347.
32. **Eastley N, Newey M, Ashford RU** (2012) Skeletal metastases—the role of the orthopaedic and spinal surgeon. *Surg Oncol*, **21**, 216–22.
33. **Lunkiewicz M, Anderson S, Havakeshian S** *et al.* (2019) Practical input on bone tumor imaging: pathological fracture, risk features, and when to contact orthopaedics. *Semin Musculoskelet Radiol*, **23**, 19–25.
34. **Nooh A, Goulding K, Isler MH** *et al.* (2018) Early improvement in pain and functional outcome but not quality of life after surgery for metastatic long bone disease. *Clin Orthop Relat Res*, **476**, 535–45.
35. **Malviya A, Gerrand C** (2012) Evidence for orthopaedic surgery in the treatment of metastatic bone disease of the extremities: a review article. *Palliat Med*, **26**(6), 788–96.

36. **Wood TJ, Racano A, Yeung H** *et al.* (2014) Surgical management of bone metastases: quality of evidence and systematic review. *Ann Surg Oncol*, **21**, 4081–9.
37. **Filippiadis D, Tutton S, Kelekis A** (2017) Pain management: the rising role of interventional oncology. *Diagn Interv Imaging*, **98**, 627–34.
38. **ClinicalTrials.gov.** *Interventional Studies, Cancer Pain*. https://clinicaltrials.gov/ct2/results?cond=Cancer+Pain&type=Intr
39. **Sopata M, Katz N, Carey W** *et al.* (2015) Efficacy and safety of tanezumab in the treatment of pain from bone metastases. *Pain*, **156**(9), 1703–13.

Chapter 4

Visceral pain

Michael Downing

Attitude

To enable each learner to:

- Demonstrate compassion and kindness—visceral pain evokes 'visceral' emotion.
- Increase awareness of its frequency and impacts—lost work, wages, quality.
- Understand the peritoneum and evolution of pain.

Skills

To enable each learner to:

- Learn the steps to clinical assessment of visceral pain.
- Be vigilant as pain evolves and adjust therapies accordingly.

Knowledge

To enable each learner to:

- Keep the complex simple, but remain aware of emerging knowledge of pain.
- Apply mechanism-based and multimodal methods to reduce pain.

Introduction

Sorting visceral pain can be daunting, given multiple organs and innervation systems, but understanding anatomy and embryology is key to clinical assessment. A mechanism-based treatment approach is best; therefore, refreshing oneself on anatomy and pathophysiology will help.

Depending on the aetiology of pain(s) and the patient's functional status, one has a wide range of potential approaches to manage visceral pain, including surgical/medical/interventional treatments, multiple medications, and opioid analgesics.

Those decisions rest with the clinician's acumen, available resources, and patient choice. What always comes into play is 'what could I do/what should I do?'

Although the term 'viscera' includes abdominal, thoracic, and pelvic organs, this chapter focuses only on abdominal pain. The reader is referred to other chapters for symptoms such as nausea (see Chapter 7) and constipation (see Chapter 8).

Case 4.1

D.H. is 36 years old, with recurrent abdominal 'discomfort' for over 1 year, along with intermittent diarrhoea and occasional small bright blood. She was treated for probable amoeba infection (living in Central America).

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She had no weight loss initially but was tired. Later episodes of sudden, severe right upper quadrant (RUQ) pain increased, so D.H. returned home. She had lost 10 kg and was very fatigued.

Case 4.2

J.M., a 42-year-old man, developed vague midline abdominal pain over several weeks. It was intermittent, hard to describe, sometimes crampy, but not severe. He was eating OK and had normal stools. After a while, the pain shifted to also include the right side of his abdomen and back. It became more persistent and sharp; it was different than his chronic back pain from a construction accident years earlier (disc injury T11). His appetite fell off, so upon examination, his doctor ordered investigations.

Question 1. How do the patients' descriptions of pain provide clues in our assessment?

The word descriptors and the ease or difficulty in locating their pain is actually very helpful to delineate the cause of pain (they used recurrent, discomfort, sudden, vague, crampy, persistent, sharp, and shifted).

Understanding visceral pain requires an awareness of peritoneal anatomy, function, innervation, and the concept of total pain, as outlined below.

Peritoneal anatomy and pain

Functions of the peritoneum

The abdominal peritoneum is composed of a single layer of mesothelial cells.

The parietal peritoneum lines the anterior, lateral, and posterior abdominal walls, under the diaphragm (supra-peritoneal), and over the pelvic cavity (infra-peritoneal).

The visceral peritoneum is the direct continuation of the parietal peritoneum which leaves the posterior abdominal cavity wall to cover the intra-abdominal viscera. The mesentery develops where two layers of the visceral peritoneum join, and the omentum is formed where two layers of the mesentery join.

The peritoneum performs several functions:

- Peritoneal fluid, approximately 50 ml, is secreted by the serosa (mesothelium, capillaries, lymphatics) into the intraperitoneal space to ensure the viscera are mobile and glide easily.
- To suspend various organs by ligaments, thereby serving also as a means of conveying blood vessels, lymphatics, and nerves to organs.
- Peritoneal coverings of the intestine tend to stick together in infection. The greater omentum, which is commonly constantly on the move, may adhere around a focus of infection to seal off and remain localized.
- Fat storage within the ligaments, mesenteries, and greater omentum.

A unique feature of the diaphragmatic parietal peritoneum are microscopic pores called *stomata*, which drain into diaphragmatic lymphatic channels (*lacunae*). The lacunae drain into the substernal lymph nodes and then into the thoracic duct. Stomata are also capable of absorbing particulate matter, including bacteria.

Visceral (serosal) pain

Visceral pain is described as vague, diffuse, and hard to localize. It is initially felt in the midline due to bilateral innervation at one of three levels, based on embryological development: foregut (epigastric), midgut (periumbilical), and hindgut (hypogastric, suprapubic) pain. Table 4.1 provides more detail, but in short, epigastric pain arises from the oesophagus to the duodenum plus the liver or spleen, whereas periumbilical pain is from the small intestine and ascending colon, and lower abdominal (hypogastric) pain occurs from the descending colon, part of the rectum, or the uterus/ovaries.

Pain is caused by distortion, inflammation, or ischaemia of a viscera. It begins in a solid or hollow viscus, although the actual tissue (e.g. hepatocytes) does not have nerve fibres. The liver is encased by a loose connective tissue capsule, called Glisson's capsule, which contains nerve endings. The visceral peritoneum overlies this—pain from hepatic stretch of the capsule causes epigastric pain initially, but then local inflammation causes a shift to RUQ pain. Nociceptors from free nerve endings and Pacinian corpuscles lie in the vascular tissue, ligaments, and muscles of an organ. Afferent pain stimuli (slow C-fibres and A-delta) arise from distension, contraction, stretching, hypoxia, chemical irritants, inflammation, and necrosis. This may gradually increase over hours to days.

Words used are vague, deep, pressure, squeezing, cramping, constant, dull, steady, bloating, or sickening. Pain is felt midline and may vary from a steady ache or vague discomfort to excruciating or colicky pain.

Visceral pain typically also involves the autonomic nervous system (ANS), with symptoms of malaise, pallor, profuse sweating, nausea, tachycardia, and hypotension. Emotional reactions from the sympathetic nervous system are common and the patient may be anxious or even may have a sense of impending doom.

Parietal (somatic) pain

This pain is well localized and made worse by movement and better when lying still. Words used are sharp, knife-like, aching, throbbing, spasm, pulling, hurts, twisting, tense, hard, irritating, grabbing, stiff, and sore.

The *parietal* peritoneum lining the anterior abdominal wall is supplied by T6–L1 nerves, similar to the muscles and skin of the abdomen. The diaphragmatic peritoneum is supplied from two sources—centrally from bilateral phrenic nerves C3, 4, 5, with pain felt in the neck, and peripherally (laterally) through the lower six thoracic nerves. Diaphragmatic muscles attach anteriorly to the xiphoid process and along the costal margins, then at the back to T5–12. In this case, pain is often worsened by respiration, coughing, or hiccups.

The *posterior* peritoneum lies against the posterior abdomen and covers some retroperitoneal organs completely (kidney, ureter, adrenal) or partially (pancreas, duodenum, colon, rectum).

The *pelvic* peritoneum covers the bladder, cervix, and lower rectum, but the uterus and ovaries are covered by the visceral peritoneum.

Other pains

- Tenesmus (rectal, bladder)—unpleasant sensation of incomplete emptying of the rectum.
- Colic (biliary, renal, ureteric, bladder).
- Reflux oesophagitis.
- Bowel obstruction.
- Carcinomatosis peritonei.
- Acute peritonitis.
- Ascites.[1]

Table 4.1 Peritoneal surfaces and organs

Organ		Peritoneal covering		Embryological origin	Referred pain
		Visceral	Parietal		
Diaphragm (not organ)		No	Yes (supra-peritoneal)	Supra-peritoneal	C3, 4, 5 central T5–12 peripheral
Liver		Yes	No (bare area)	**Foregut** *Epigastric pain*	T5–9 right
Oesophagus		Yes	No		T4–6
Stomach		Yes	No		T5–8 left
Gall bladder		Yes	No		T6–9
Pancreas	Body, head	No	Yes (retroperitoneal)		T5–9
	Tail	Yes	No		T5–9
Omentum		Yes	No		T7–10
Spleen		Yes	No		T6–8 left
Duodenum	First, fourth part	Yes	No		T8–11?? 5–10
	Second, third part	No	Yes (retroperitoneal)	**Midgut** *Periumbilical pain*	T8–11
Jejunum, ileum		Yes	No		T8–12 Symp T5–9
Colon	Caecum/appendix	Yes	No		T10–12
	Ascending	No	Yes (retroperitoneal)		T10–12
	Transverse 2/3	Yes	No		T8–12
	Distal 1/3 trans	No	Yes (retroperitoneal)	**Hindgut** *Hypogastric pain*	Symp L1, 2
	Descending	No			Para S2, 3, 4
	Sigmoid	Yes	No		Upper L1, 2 Lower S2–4
Rectum	Upper 1/3 Middle 1/3 Lower 1/3	Yes No No	No Yes (retroperitoneal) Yes (infra-peritoneal)		Symp L1, 2 Para S2–4
Adrenal		No	Yes (retroperitoneal)	Retroperitoneal	T5–11
Kidney		No	Yes (retroperitoneal)		T5–12
Ureter		No	Yes (retroperitoneal)		T12–L2
Bladder		No	Yes (infra-peritoneal)	Infra-peritoneal	Symp L1, 2 Para S2–4
Pelvis	Uterus/ovary	Yes	No		T10–L1 Para S2–4
	Cervix	No	Yes (infra-peritoneal)		S2–4
	Vagina	No	Yes (infra-peritoneal)		
	Anus	No			
	Scrotum	No			
	Testicle	No			

para, parasympathetic; symp, sympathetic.

Referred pain

Referred pain is 'visceral pain perceived as somatic pain located by 'dermatomes' of the skin. It produces symptoms, not signs. It occurs when pain from visceral nociceptors recurs frequently or is more intense or prolonged, so the location becomes more specific and felt in areas on the body surface (see Figure 4.1).

This is due to viscerosomatic convergence[2] of afferent impulses from the viscera, along with parietal pain sensation (dermatomes) at the same level of entry into the spinal cord dorsal horn. This leads to increased sensation and cord sensitization of the same segment. As there are many more neurons from the skin, compared to afferent visceral or parietal fibres, pain gets 'misinterpreted' to these referred areas (Ruch's hypothesis).

The dermatome may progressively develop over hours to days, so the person 'feels' the pain at a distance. Referred pain is sharper, better localized, and less likely to be accompanied by autonomic or emotional signs.

Referred pain is different than 'radiation' of pain, such as when a bulging disc presses on a nerve root causing pain in the dermatome of the affected nerve (e.g. sciatica).

Total pain

Total pain is always an element of physical pain. There are seven 'P's of pain: physical, emotional, intellectual, interpersonal, spiritual, financial, and bureaucratic.[3] Both D.H. and J.M. are young, so cancer itself and chronic pain are entwined with emotional worry, frustration, and depression. Their inability to work places financial pressures on them, and D.H.'s cancer recurrence with bowel obstruction and later hepatic progression, despite chemotherapy, is most distressing.

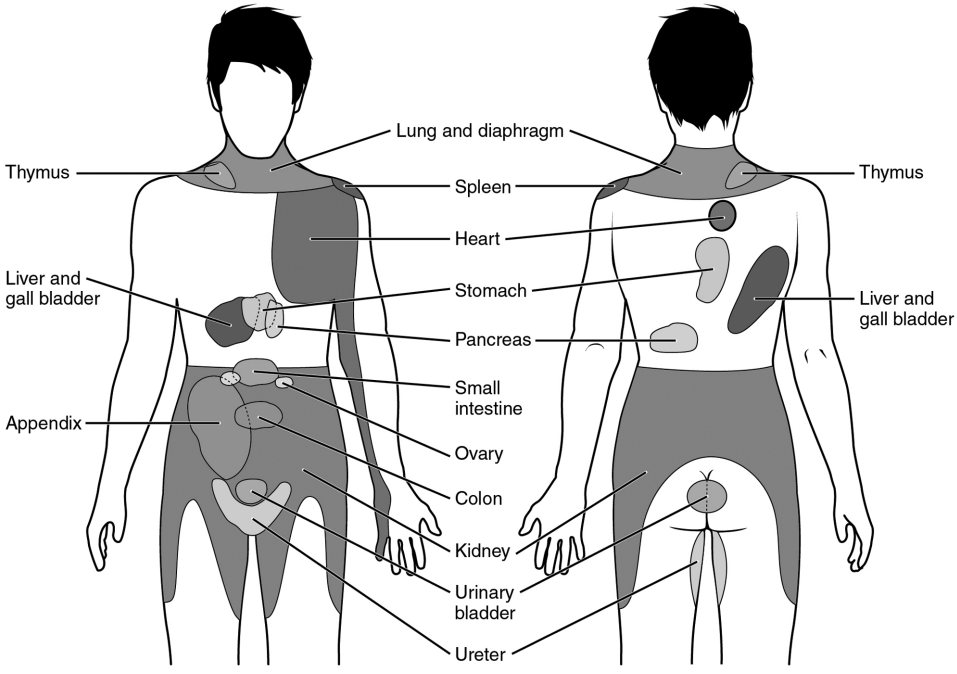


Fig. 4.1 Referred pain.

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The gut, brain, and vagus (X) nerve are connected. Vagal afferents carrying visceral nociception divide in the brainstem. The spinothalamic tract provides afferents from the thalamus to the somatosensory cortex for pain quality, intensity, and location.[4] The spinoreticular tract projects to the anterior cingulate cortex (ACC) and beyond for emotional and autonomic output interaction (satiety, fullness, dread, nausea), and also the spinomesencephalic to the MCC for cognitive and motor output.[5] These visceral afferents may trigger fight/flight sympathetic outflow; indeed, our feelings get expressed viscerally.

Question 2. What important features would you look for on physical examination?

- Firstly, rule out an acute abdomen (peritonitis):
  - Either lying rigidly still or very restless.
  - Guarding.
  - Rigidity.
  - Sharp pain on palpation.
  - Rebound tenderness.
  - Quiet or absent bowel sounds.
- Is it visceral only—foregut, midgut, hindgut?
  - Few signs—possible tenderness on deep palpation of organ.
  - Vague; hard to describe and locate.
- Are there 'autonomic' signs of malaise, nausea, sweating, dread, etc.?
- Is there 'referred' pain?—no significant findings (e.g. shoulder normal).
- Evidence of parietal peritoneal inflammation?
  - Pain is more localized.
  - Tender on local palpation.
  - Possible guarding, but no rebound tenderness.
  - ± psoas sign.
- Finally, is there only one pain, even if it changes character, or does the patient have several things happening? In advanced illness, it is common to see four or more different pain issues.

Question 3. What is the differential diagnosis and why did the pain(s) move?

Case 4.1 (continued)

A computed tomography (CT) scan showed multiple hepatic metastases, and colonoscopy revealed adenocarcinoma of the caecum. Surgery was not possible, so D.H. started chemotherapy with capecitabine, but at 75% of the dose due to anaemia/fatigue (haemoglobin 84, albumin 40). A palliative consult was requested. The RUQ pain was dull, constant, and diffusely tender on palpation. There was pain in the right shoulder tip, worse with cough or deep inspiration. Some pain was present in the right lumbar flank.

For D.H., the diagnosis of extensive hepatic metastases was not good, but she was young. Pain in the RUQ reflects visceral peritoneal capsule stretch (Glisson) and the referred shoulder pain is due to diaphragmatic parietal irritation. The 'bare area of the liver' is in direct contact posteriorly to the diaphragm, so tumour

may also cause T7–9 somatic pain. She was taking metoclopramide for nausea, vomiting, and hiccups. It was switched to haloperidol 0.5 mg twice daily and started on hydromorphone controlled-release (HMC) 3 mg every 12 hours (q12h) and short-acting 1 mg q4h PRN.

Several months later: a new periumbilical pain developed, with cramping and abdominal distension; there was little flatus, and stools were reduced, but no blood. She was treated with intravenous (IV) fluids and dexamethasone 4 mg daily, and metoclopramide was restarted. Her condition worsened to a partial small bowel obstruction; she underwent right hemicolectomy and recovered to continue chemotherapy. The RUQ and shoulder pains were in good control on HMC 9 mg q12h.

Over next 12 months: D.H. remained in good pain control. However, fatigue, especially after chemotherapy, was severe. She responded to methylphenidate initially and was later changed to modafinil; escitalopram was added for depression. Later, abdominal pain gradually worsened with hepatomegaly and frequent shoulder pain; chemotherapy was stopped. Hydromorphone was titrated to HMC 12 mg q12h, and dexamethasone was increased to 8 mg daily. Pain remained controlled, but progressive ascites caused pain on movement; repeat paracenteses provided temporary relief. She gradually declined, becoming bed-bound and died 30 months following diagnosis.

Case 4.2 (continued)

J.M. underwent resection for 11-cm adenocarcinoma of the colon at the hepatic flexure with right hemicolectomy. The surgeon noted the tumour was attached to the lateral abdominal wall. There was also 'inflammatory adhesions over the duodenum and right kidney', but the surgeon felt no tumour.

His first difficulty was vague abdominal pain and periodic bloating. This reflects visceral peritoneal inflammation in the hepatic flexure ('midgut' ascending colon). Pain then changed character to the right flank (parietal peritoneum). During surgical resection at the hepatic flexure, the tumour had invaded the lateral abdominal wall (parietal), which explains localized flank pain. Adhesions to the duodenum and mesentery were lysed but did not appear cancerous.

One month later: J.M. became bloated and had periumbilical cramping pain, along with nausea. Hours later, the pain was terrible and constant, and he had to lie still. Imaging showed a volvulus with bowel obstruction, and J.M. underwent laparoscopic surgery for lysis of adhesions and release of the volvulus. Unfortunately, he had a serious post-operative wound infection delaying recovery.

One year later: J.M. recovered well but has ongoing severe pains around the surgical scar, RUQ, and right flank. The pain is debilitating and he is unable to do physical work in construction. He is on cancer surveillance. There are four pains: incisional scar neuropathic pain, intermittent RUQ/flank pain, postprandial epigastric pain, and chronic back (disc) pain.

He was already on gabapentin 900 mg three times daily (prior disc injury) and a fentanyl 50 mcg patch every 3 days (q3days), with morphine breakthrough doses. What other medications or steps are appropriate?

Question 4. What is happening and how would you manage these persistent pains?

J.M.'s vertical midline scar is exquisitely tender to light touch (allodynia) and on bending over, and is burning in quality. The epigastric abdominal pain occurs 20 minutes after oral intake. He gets nauseated and may vomit. Pain is severe, cramping, and located in the epigastrium, but also in the RUQ/flank.

He was rotated through several opioids and given gabapentin, non-steroidal anti-inflammatory drugs (NSAIDs), buscopan, metoclopramide, antidepressants, and cannabis, with little success.

The fentanyl patch was increased to 75 mcg every 72 hours (q72h). Multiple breakthrough doses helped, but some feel this may be drug-seeking or opioid hyperalgesia. Repeat CT scans, lab tests, and colonoscopy were normal.

The chronic RUQ/flank pain is due to peritoneum and abdominal wall damage from original tumour invasion, surgery x2, and post-operative wound infection, resulting in fibrous scar tissue with abdominal wall, nerve, and muscle damage.

The postprandial epigastric pain and nausea are likely duodenal adhesions and damage during surgery. Metoclopramide exacerbated his pain and nausea, so now he only uses dimenhydrinate PRN. Prior adhesions caused bowel volvulus.

Today, he is tapering fentanyl now at 12 mcg/hour (consider methadone) and taking diclofenac, acetaminophen, trimipramine, and gabapentin. A test splanchnic sympathetic block did not help, but abdominal planus lidocaine infusions or coeliac block will be considered. Periodic local lidocaine/saline injections are quite successful for scar neuropathy. Coeliac block may need to be considered. He is awaiting a surgical consult for exploratory laparoscopy for duodenal pain and possible adhesion lysis or even bypass. He continues a chronic pain education coping programme and physiotherapy stepped exercises.

Let's be a little amazed

We are so unaware of what is happening inside our body and the complexity. Let us pause for a moment.

Question 5a. How much fluid is in the gut?

The amount of fluid in the bowel and its daily flux is large.[6] Upwards of 9–10 litres of fluid enter the gut each day from several sources:

- Oral dietary intake: 2000–3000 ml/day.
- Saliva: 1000–2000 ml.
- Gastric secretion: 1000–2000 ml.
- Bile: 500–1000 ml.
- Pancreatic secretion: 1000–2000 ml.
- Intestinal secretion: 1000–2000 ml.

Most of this fluid is reabsorbed in the jejunum and ileum. About 1500 ml/day enters the colon; over 1 litre is further absorbed, with only 200 ml remaining in faecal content. Thus, approximately 98% of fluid is removed each day. This net fluid movement in/out of the bowel is referred to as daily cycling or enterosystemic circulation between the gut and the circulation. If a bowel obstruction occurs at any level, fluid accumulates, even if oral intake is minimal, causing distension, nausea, and cramping pain.

Question 5b. How many bacteria are in the gut? What is the microbiome?

The gut microbiome is the name given to the microbe population living in our intestine. It contains approximately 38 trillion microorganisms, including at least 1000 different species.[7]

In comparison, the total cell content in our body contains approximately 30 trillion cells, with 84% being red blood cells (RBCs). The 38 trillion bacteria is 1.3 times more than human body cells. The total bacteria population weighs only 0.2 kg or 0.3% of total body weight. As expected,

there are fewer bacteria in the stomach (10^7) than in the ileum (10^{11}) or colon (10^{14}). By the way, saliva is similar to the ileum at 10^{11}.[8]

The microbiome interacts with the array of gastrointestinal interactions to digest and absorb nutrients via the enteric nervous system (ENS).

Question 5c. What is the gut epithelial turnover?

There are about 10 billion (10^{10}) epithelial cells shed each day from the small intestine alone. Between fluid, bacteria, and the epithelium, then even dying patients unable to eat or drink still produce some stool content.

Question 5d. What is the enteric nervous system?

The myenteric plexus is the major nerve network in the gastrointestinal tract and controls gastrointestinal tract motility (Auerbach's plexus) and digestion (Meissner's plexus). There are both parasympathetic and sympathetic innervations of longitudinal and circular muscle layers. The ENS is 70% motor and 30% sensory.

Fibres originate in the medulla oblongata and travel in the vagus nerve. The ENS functions autonomously but is also connected with the ANS. There are upwards of 500 million neurons and over 30 different neurotransmitters (e.g. acetylcholine, dopamine, serotonin). More than 90% of the body's serotonin lies in the gut, as well as 50% of total dopamine.

Interestingly the ENS has taste receptors similar to the tongue. The TAS1R3 receptor senses 'sweetness' on the tongue and the ENS senses 'glucose' in the gut.

The myenteric plexus 'talks' and interacts with the central nervous system about the state of the gut—general signals of hunger, satiety, fullness, nausea, etc. travel through the parasympathetic (vagus nerve) and relay, for example, hormone needs to the hypothalamic tract to assist digestion (parasympathetic 'rest/digest' signalling). If there is excess bowel distension or chemical irritants present, then nociceptive signals from free nerve endings of C- and A-delta fibres are activated through spinal nerves (sympathetic 'flight/flight').[4] If nociception is sustained, 'visceral sensitization' develops, similar to the peripheral system, with upregulation and spread of signals. There is evidence that neuropathic upregulation can occur,[4] even involving N-methyl-D-aspartate (NMDA) receptors.[9]

One way the gut microbiota communicates with the nervous systems is through intrinsic primary afferent neurons (IPANs) that reach deep into the gut mucosa and respond to changes in the gut lumen.[4] IPANs are transducers and convert physiological stimuli into electrical signals. They influence the patterns of motility, secretion of fluid across the mucosal epithelium, and local blood flow in the intestines.[10]

Why go through all this anatomy? Sense-making and treatment

It is beyond the scope of this chapter to discuss all diseases and treatments. If the anatomy and likely causes of pain are recognized, then treatment approaches become clear.

Principles

- Keeping it simple.
  - What is going on? Think 'stretch, inflammation, ischaemia', and apply treatment accordingly.
  - Can I 'fix' it? If so, should I? Consider benefit versus burden.

- If able to fix (remove/bypass/shrink), it is generally good as reduces drug burden. If not, then target drugs.
- If treatment is started, it does not mean it must continue (patient involvement).

Treatment approaches

- *Interventional treatment*—surgery, stent, radiation/ablation, chemotherapy, drainage (paracentesis, G-tube, pigtail), nerve block (hypogastric, coeliac, sympathetic), urostomy, lithotripsy, etc.
- *Medications*. If not 'fixable', then provide pain relief using mechanism-based treatment. It is often necessary to use multiple medications.
  - Analgesics—non-opioid, opioid.
  - Anaesthetic interventional nerve blocks.
  - Anti-inflammatory NSAIDs.
  - Anticholinergic (bowel, bladder spasm).
  - Antidiarrhoeal (loperamide, diphenoxylate, octreotide, opioid).
  - Anti-haemorrhoidal.
  - Anti-anginal (anal fissure).
  - Antibiotics.
  - Antispasmodics (B&O, oxybutynin).
  - Anxiolytic.
  - Cannabis.
  - Enzymes—Creon®, lipase.
  - Gastroprotectant—H2 antagonist, proton pump inhibitor (PPI).
  - Laxatives.
  - Neuropathic—anticonvulsant, antidepressant.
  - Octreotide.
  - Probiotic.
  - Prokinetics.
  - Sedative/anxiolytics.
  - Steroids.
  - Special targeted therapies:
    - Serotonin $5HT_4$ agonist, e.g. tegaserod.
    - $5HT_3$ antagonist—alosetron (e.g. irritable bowel syndrome).
    - 'mab' for Crohn's disease, inflammatory bowel disease (IBD), and ulcerative colitis (UC).

Special considerations

Some illnesses are long-standing and not usually viewed as 'palliative'. However, the recent 'palliative approach' model considers more integrated care for patients earlier in their disease trajectory who are not at end of life. Gastrointestinal neuromuscular diseases are good examples. Visceral hypersensitivity is regarded as the pathognomonic feature of functional gastrointestinal disease (FGID), such as IBD, Crohn's disease, and UC, with distinct structural lesions or biochemical abnormalities.[11]

The future

The gut microbiome appears as an essential component of immune and metabolic health, but also seems to influence the development of diseases of the ENS and central nervous system, including motility disorders, behavioural disorders, neurodegenerative disease, and others.[12]

Unlike previously thought, both peripheral and central sensitizations have been demonstrated as mechanisms in visceral pain.[4] New treatments may emerge for visceral sensitization, including receptor targets such as ion channels, adenosine triphosphate (ATP)-gated channels P2X, protease-activated transient receptor potential vanilloid 1 (TRPV-1), acid-sensing ion channels (ASICs), and serotonin. Cannabinoids, or derivatives, may prove of significant benefit for pain, nausea, and appetite for gastrointestinal issues.

Finally, a new concept referred to as the 'chronification' and 'stickiness' of pain[13] may bring important new approaches.

Pearls

- Clues—pay close attention to where pain first began and what it felt like. Then, over hours to days, how did it change?
- Think—stretch, ischaemia, and inflammation.
- Mechanism-based treatment is the best approach—remove (disease-modifying) and relieve (symptom-modifying).
- Total pain is especially real ('what is your gut saying?') with gastrointestinal pain.

References

1. **Hicks A**, **Chou J**, **Capanu M** (2016) Pancreas adenocarcinoma: ascites, clinical manifestations, and management implications. *Clin Colorectal Cancer*, **15**(4), 360–8.
2. **Sikandar S**, **Dickenson AH** (2012) Visceral pain—the ins and outs, the ups and downs. *Curr Opin Support Palliat Care*, **6**(1), 17–26.
3. **Downing M** (2006) 7 'P's of pain. In: Downing M, Wainwright W (eds) *Medical Care of the Dying*, 4th edn, pp. 94–7. Victoria Hospice Society, Victoria, BC.
4. **Knowles C**, **Aziz Q** (2009) Basic and clinical aspects of gastrointestinal pain. *Pain*, **141**, 191–209.
5. **Stevens FL**, **Hurley RA**, **Taber KH** (2011) Anterior cingulate cortex: unique role in cognition and emotion. *J Neuropsychiatry Clin Neurosci*, **23**(2), 121–5.
6. **Brandis K.** *Fluid Physiology*. https://www.anaesthesiamcq.com/FluidBook/fl3_5.php
7. **Gut Microbiota for Health**. *Gut Microbiota Info*. https://www.gutmicrobiotaforhealth.com/en/about-gut-microbiota-info
8. **Sender R**, **Fuchs S**, **Milo R** (2016) Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol*, **14**(8), e1002533.
9. **Kolhekar R**, **Gebhart GF** (1996) Modulation of spinal visceral nociceptive transmission by NMDA receptor activation in the rat. *J Neurophysiol*, **75**, 2344–55.
10. **Furness J**, **Jones C**, **Nurgal K**, **Clerc N** (2004) Intrinsic primary afferent neurons and nerve circuits within the intestine. *Prog Neurobiol*, **72**(2), 143–64.
11. **Wouters MM**, **Vicario M**, **Santos J** (2016) The role of mast cells in functional GI disorders. *Gut*, **65**(1), 155–68.
12. **Strandwitz P.** Neurotransmitter modulation by the gut microbiota. *Brain Res*, **1693**(Pt B), 128–33.
13. **Borsook D**, **Youssefa AM**, **Simonse L**, **Elmanf I**, **Ecclestong C** (2018) When pain gets stuck: the evolution of pain chronification and treatment resistance. *Pain*, **159**(12), 2421–36.

Chapter 5

Neuropathic pain

Srini Chary, Anne B. Boyle, Leonie M. Herx, and Susan MacDonald

Attitude

To enable each learner to:

- Respect pain as a subjective experience.
- Understand that the patient is the best judge of the response to treatment.
- Understand the importance of ongoing research in this field.

Skills

To enable each learner to:

- Assess and determine the probable cause of nervous system pain.
- Identify the possible treatments for nervous system pain.

Knowledge

To enable each learner to:

- Understand the general medications used in neuropathic pain management.
- Understand current taxonomy.

Case 5.1

K.B. is a 62-year-old taxi driver who presented to his family doctor 5 months ago with cough, weight loss, and fatigue. Investigations revealed Stage 4 adenocarcinoma of the lung, with metastasis to the liver, ribs, and thoracic vertebrae (T11 and T12). After long discussions with his partner, his two adult children, and his oncologist, he decided not to pursue active treatment of the cancer. He did have five fractions of radiotherapy to the primary lesion for mild haemoptysis. Initially, he had no pain. Although he was fatigued, he and his wife elected to go on a 3-week Mediterranean cruise they had always wanted. Four days before returning home, K.B. noticed that his ribs (right anterior, mid-clavicular ribs 8 and 9) were aching and that his clothes seemed to irritate him in that area. He took acetaminophen 1000 mg po four times a day, without benefit. On his return, his family physician started him on acetaminophen with codeine 30 mg four times a day. This too was ineffective.

K.B. describes the pain as a 5 or 6 out of 10. It disturbs his sleep (hard to fall asleep, wakes him if he rolls over onto his right side). It does not radiate and there is no paraesthesiae associated with it (no numbness or tingling). He describes the pain as 'gnawing' and constant. On examination, there is no sign of skin irritation or infection. His ribs are very tender to touch, and just light touch to the surrounding skin is uncomfortable.

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Question 1. What type of pain is K.B. experiencing?

Pain can be described temporally (how long the patient has had it—acute or chronic) and by cause (what anatomical structures are involved). There are also many factors involved in the experience of pain (see Question 4). All are important in determining the approach to treatment.

Pain that is acute often has associated sympathetic nervous system factors—patients look uncomfortable and may have diaphoresis and a rapid heart rate. Those sympathetic factors disappear with time, and patients with chronic pain may look and act as if they are not in pain. The late Dr Daniel Brookoff in 2000 explained much of present knowledge relating to pain.[1,2]

Anatomically, pain can be sorted into somatic, visceral, and neuropathic types. Simply put, somatic pain is pain of the soma (firm tissues of the body such as bone, muscle, and skin), while visceral pain is that of the soft tissues (internal organs). The nervous innervation of the bone and skin is different than that of the viscera, which leads to differences in how the body perceives the pain and the ability to determine location. The skin, for example, has specific nerve innervation—if a patient has a laceration to his leg, he will be able to point to the exact spot where there is pain. The viscera have more generalized nervous innervation—a patient is generally not able to identify the exact location in their liver where the pain is but can identify that the right upper quadrant of their abdomen is uncomfortable (see Chapter 3 on somatic pain and Chapter 4 on visceral pain).

Neuropathic pain arises in the nervous system. It is different from somatic or visceral pain in a number of ways. Often, patients will complain of paraesthesiae associated with the pain: numbness, tingling, pins and needles sensation, or electric shock-like pain.[3] The pain may be more severe and more challenging to treat. Nerve pain also changes over time, with nerve pathways becoming 'rearranged'. This results in entrenched pain that can be impossible to eradicate.

Previously called 'opioid-resistant or dysesthetic pain', neuropathic pain is common when there is central or peripheral nerve injury in the form of local pressure, severance of nerve, demyelination, or neuromas. Toxicity from chemotherapy, or antibiotics, and microvascular damage may also lead to peripheral sensory neuropathy. A likely mechanism is voltage-gated sodium channel modification in peripheral nerves with sensitization of the dorsal horn.[4] Present evidence also suggests a role for colony-stimulating factor 1, adenosine triphosphate (ATP), and brain-derived neurotrophic factor. Neuroexcitatory processes are enhanced and inhibitory processes are attenuated in the spinal dorsal horn and somatosensory system. The signs and symptoms include allodynia (pain in response to an innocuous stimulus), hyperalgesia (increased pain in response to a noxious stimulus), and spontaneous pain (electric shock-like or shooting pain).

Evidence suggests that persistent pain lasting more than 3 months ('chronic pain') leads to activation of N-methyl-D-aspartate (NMDA) receptors, along with changes in alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and release of neuroexcitatory glutamate in the synapse.[1] In chronic pain, this manifests as 'neuroplasticity'; the brain 'learns' and new pain pathways are created. In 2018, the International Association for the Study of Pain (IASP) added *nociplastic pain* to the taxonomy of pain in relation to central nervous system (CNS) sensitization. It was considered as patients with cancer who have palliative care needs often have multiple possible causes of neuropathic pain. They may have nerve damage from chemotherapy, surgery, radiation, or other injury. There may be a tumour pressing on a nerve or growing centrally in the brain. And they may have comorbid conditions such as diabetes that have contributed to a neuropathy. Functional magnetic resonance imaging (fMRI) of the brain can show amplification of pain signals between the thalamus and the limbic systems of individuals with chronic pain and CNS sensitization.[5]

Question 2. How would you approach managing K.B.'s pain?

A thorough history and physical examination are important in the management of all types of pain. The DN4 questionnaire[6] is helpful in confirming a diagnosis of neuropathic pain. You must also ensure there are no signs of infection. For example, patients who are immunocompromised are at risk of herpes zoster outbreaks. Shingles often presents with dysesthesia before the rash.

K.B. has features of neuropathic pain—the sensitivity he describes to gentle touch is indicative of allodynia. He also has features of somatic pain from his bony metastasis in the area of his pain.

The family physician considers the pain to be somatic (from the metastatic bone lesions) with a neuropathic component. She starts the patient on amitriptyline 10 mg po nightly before bed and instructs him that this medication may make him a little sleepy but should help the nerve component of the pain. She also prescribes morphine 5 mg po q2–4h PRN and asks the patient to take the medication as needed to reduce the pain down to a 2 or 3 out of 10 on a pain severity scale. K.B. is instructed to keep a diary of how many pills he needs and when he takes them. The doctor warns K.B. that if he becomes sleepy or confused to stop the medication and call her. She also advises that he should not drive until he is deemed safe to drive once he reaches a stable dose. She gives K.B. a prescription for a laxative as well.

Case 5.1 (continued)

Forty-eight hours later, the physician calls K.B. to see how he is doing. He relates that he took six tablets on Day 1 and eight tablets on Day 2. His pain has reduced to a 3/10 and he was able to get some sleep the previous night. However, his shirt or the bed sheets touching his skin really bother him and this has not improved with the morphine.

While opioids have a role in the treatment of neuropathic pain, they are considered second line after other medications, often referred to as adjuvants or co-analgesics. For second-line management, any opioid may be used, following the same cautious strategies that apply to treating any pain (start low, go slow, and titrate upwards using breakthrough dose usage as a guide). Methadone, in particular, may be a better option specifically for neuropathic pain and can also be used as an adjuvant in low doses to reduce overall opioid use (see Chapter 31 on methadone for additional information).

Question 3. What adjuvant/co-analgesic medications are indicated to manage neuropathic pain?

Medications for neuropathic pain can generally be classified in three main groups: antidepressants, anticonvulsants, and topicals. Other therapies under study will also be discussed briefly. Tricyclic antidepressants (TCAs) have been around for decades.[7] The most commonly used TCAs for pain are amitriptyline, desipramine, and nortriptyline. Doses required for treating neuropathic pain are generally much lower than what is needed for depression. Commonly, one starts with a low dose and titrates upwards on a weekly basis until the patient either finds some relief or cannot tolerate the side effects. Some patients can be started on as low as 10 mg of amitriptyline and gain benefit, while some will require 50–100 mg to be effective. TCAs, while effective and inexpensive, have side effects, which some patients find intolerable. These include dry mouth, blurred vision, and sedation.[8–10] The sedative side effect may be helpful for some patients, as many people with neuropathic pain have trouble sleeping. The medication is generally given as a once-a-day dose at bedtime. TCAs should be used with great caution in those with cardiac arrhythmias, congestive heart failure, orthostatic hypotension, urinary retention, or angle-closure glaucoma.[11]

Other antidepressants are sometimes used in neuropathic pain.[12] Serotonin–noradrenaline (norepinephrine) reuptake inhibitors (SNRIs), for example duloxetine and venlafaxine, are used for low back pain, diabetic neuropathy, post-herpetic neuralgia, and polyneuropathy.[13] Selective serotonin reuptake inhibitors (SSRIs) have not been found to be as effective in treating neuropathic pain.

Gabapentinoids, gabapentin, and pregabalin are anticonvulsants commonly used to treat neuropathic pain. They work on calcium channels in the brain and spinal cord. While their mode of action may be similar, they have different pharmacodynamics, in particular different absorption and bioavailability. Gabapentinoids have less likelihood of interacting with other medications than TCAs and can therefore be used in patients who are already taking many other medications. They are generally well tolerated, but common side effects can include dizziness, somnolence, and oedema that can be especially problematic in the elderly. It is critical to remember that these medications are eliminated renally and therefore must be renally dosed. This is especially important in the palliative care population.[13,14]

Topical preparations can be helpful for neuropathic pain originating from superficial peripheral nerves. These include capsaicin cream, which can be helpful for conditions like post-herpetic neuralgia, and topical lidocaine which has also been shown to be effective.[14,15]

In Canada, tetrahydrocannabinol (THC) or nabiximols 1–2 sprays every 2 hours (q2h) PRN, up to four sprays a day, have been approved for neuropathic pain associated with multiple sclerosis (MS). In Canada, cannabinoids are considered third-line treatment for pharmacologic management of chronic neuropathic pain[15,16] (also see Chapter 33 on medical cannabis).

Other compounds are being evaluated for their analgesic potential and newer pharmaceuticals are in development for neuropathic pain. Currently, there is little convincing evidence to suggest the routine use of substances like tetrodotoxin,[12,17] ketamine,[16] dextromethorphan, memantine, bupropion, lamotrigine, and tapentadol. However, in patients where standard therapy has not been effective, these agents may have some utility. It is recommended this be done in consultation with a palliative care or pain specialist. More research and robust clinical trials are needed.

Case 5.1 (continued)

K.B. is encouraged to continue with amitriptyline, as it can take several weeks before the benefit is noticed. He is advised of the side effects of this medication and is instructed to increase to 25 mg po every night at bedtime (qhs), and up to 50 mg po qhs after 2 weeks if there is no improvement and he is tolerating the medication well. At the same time, he is rotated from the immediate-release formulation of morphine to a long-acting version for convenience. He is now taking 15 mg of long-acting morphine twice a day.

K.B. follows the instructions. Within 3 weeks, he is feeling better. His pain is under good control; he rarely needs to take any breakthrough morphine, and he sleeps well.

Question 4. What other information would help you in developing his treatment strategy and how would you approach it?

In any given individual, pain perception and expression are influenced by genetics, epigenetic effects from past experiences, and psychosocial, spiritual, and physical factors (see Figure 5.1). Genetics and epigenetic effects can also play a role in mental health, coping, and substance use disorder.[18,19] A past history of physical, psychological, or sexual trauma can lead to 'epigenetic

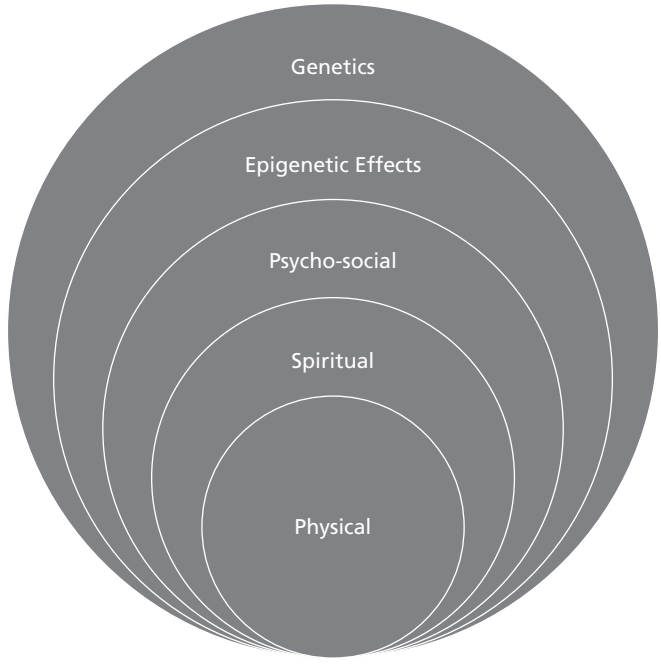


Fig. 5.1 Pain: genetics, epigenetic effects from past experiences, and bio-psychosocial and spirituality influences pain perception and expression in a given individual.

effects', which can result in genomic alteration and become generational.[20] It is very important on history taking to ask about both personal and family history of trauma, mental health issues, and substance use disorder. Patients at risk of opioid use disorder who require opioids for management should be screened using a standardized assessment tool, for example the Opioid Risk Tool (ORT).[20]

K.B. had a completed ORT assessment. This tool identified a family history of exposure to alcohol use disorder, as well as some physical and psychological trauma secondary to living in foster care as a child. He denied current or historical street drug usage, sexual abuse, or gambling. He was stratified as moderate risk for opioid use disorder.

Involving the patient in the development of their management plan is important. A goal for pain reduction should be set. Complete reduction of pain to 0/10 is not realistic and patients need to understand that a 25–30% reduction or a decrease of 2 points on the numeric pain scale is considered a success. It would be helpful to gain the patient's understanding of his condition. What is he concerned about? What does he hope for? How are his mental state and understanding of his situation affecting how he takes his medications and how he is coping with his pain? K.B.'s past history (disruptive childhood, poor coping, etc.) may impact his care. Supportive counselling during the process of medication titration may also be effective. The prognosis of his disease and goals of care discussions may affect treatments or investigations that he is willing or unwilling to undergo.

Case 5.1 (continued)

About 4 months later, K.B. calls to say that he has developed new low back pain. He has had it for a month. It was mild initially and he did not think much of it; however, it has worsened and changed. What was just a low 'ache' is now 'pain' and there is now the occasional shock-like sensation that goes down the back of his leg

and into his ankle. K.B. has self-medicated with his breakthrough morphine 5 mg po q1–2h PRN. He takes 4–6 breakthroughs per day but rates his overall severity score at 7–8/10. He is worried about this new pain and about how much pain medication he is taking. Yesterday and today, he stumbled going up the stairs to his front door. He says his right foot and leg seem 'weak'. He denies numbness in the groin, rashes, incontinence, or temperature change.

Question 5. What problems are you worried about for K.B. and how would you approach it?

This patient is at risk of spinal cord compression, and a thorough history and physical examination must be completed to rule this out. If evaluation yields a high index of suspicion, urgent imaging must be done to assess the cord.

K.B.'s history and physical examination confirmed weakness in his right leg. Urgent magnetic resonance imaging (MRI) confirmed new L1 and L2 metastases, in addition to previous thoracic metastases. There was an epidural tumour, with evidence of early spinal cord compression in the L1–L3 region.

Treatment of the spinal cord compression with urgent radiation therapy and high-dose dexamethasone should be offered to address his current neurological symptoms, as well as to prevent worsening of the condition. Post-radiation, dexamethasone is then tapered to stop, if tolerated.

Question 6. What should you be concerned about when a patient's opioid dose has been rapidly escalating?

If a patient has excessive increases in their opioid use that does not appear to correlate with clinical changes or advancing disease, opioid use disorder should be considered. Uncommonly, a patient can also develop opioid-induced tolerance and hyperalgesia,[21–23] a clinical situation where the pain actually worsens as the amount of opioid increases. Hyperalgesia is associated with the NMDA receptor and glutamate transmission. When either of these two concerns are observed (excessive increase with no benefit or worsening pain with increased doses of opioids), the clinician should include tolerance and hyperalgesia in the differential diagnosis (see Chapter 2).

K.B.'s prescribed opioid use has been escalating. However, this appears in keeping with the clinical changes and progression of the disease.

Case 5.1 continued

K.B. has urgent radiotherapy to treat his cord compression. He requires high-dose steroids initially, but this is tapered after the radiation is complete. The steroids caused his blood sugars to temporarily rise into the 20s and these were managed while elevated.

While the radiotherapy was effective in stopping further nerve damage in the spine and K.B. has not progressed to paralysis, the pain has only been marginally improved. His opioids were carefully titrated upwards over time. He is now on long-acting morphine 100 mg po q12h and his amitriptyline was titrated to 150 mg daily. He developed some mild myoclonus and confusion and was rotated off the morphine to hydromorphone. He responded relatively well to this rotation and 25% dose reduction. He rated his pain as 4–5 out of 10 in severity. K.B. also found the side effects of amitriptyline very bothersome (dry mouth, sleepiness) and asked to try something else.

Question 7. What non-pharmacologic treatments would be of benefit?

Medications are only part of pain management, and neuropathic pain is no exception. Patients should have the benefit of understanding why they are experiencing pain. Some patients associate pain with disease advancement and this is not always true. Understanding how the body heals, how nerves respond to injury, and that the severity of pain may not correlate with the degree of disease can help patients cope. As well, a thorough understanding of how medications work and how best to take them is a key component in a patient's care and disease management.

Heat, ice, or transcutaneous electrical nerve stimulation (TENS) can have benefit for some patients. Physiotherapy to reduce stiffness and swelling, or improve mobility and tone, can sometimes provide relief. There might be reduced pain from learning how to move differently or using equipment/splints/braces. Meditation and biofeedback may also have a place in the therapeutic armamentarium of some patients.

For difficult-to-control neuropathic pain, neuraxial procedural interventions and nerve blocks can also be considered (see Chapter 34 on interventional analgesic techniques).

Case 5.1 (continued)

K.B. did well at home for a number of weeks but was then readmitted in a pain crisis. He wished no further tests or investigations. His medications were adjusted and he is now on dexamethasone, gabapentin, venlafaxine, and a fentanyl patient-controlled analgesia (PCA). His morphine equivalent daily dose (MEDD) was 400 mg. After discussion with K.B. and his family, he agreed to consider adjuvant low-dose methadone, with no changes in his present pain medications. Identified goals were restful sleep at night, mood being better than neutral, reduction of baseline and breakthrough pain by 30%, and if benefit was noted with methadone, a gradual reduction of other opioids and gabapentin as he found he was sleepy and dizzy.

He was started on methadone 2.5 mg po q12h. After 3 days, it was increased to 2.5 mg po every 8 hours (q8h). Initially, he did not notice any benefit or adverse effects. Around the fourth day, he expressed his nighttime sleep was better and around the tenth day, his methadone dose was increased to 5 mg po q8h and he felt his allodynia and shocks had improved.[24,25]

He agreed to reduce the continuous dose of fentanyl and was able to halve it over 3 days and his gabapentin was decreased to 100 mg po three times a day.

Summary

Cancer and non-cancer patients with chronic pain may have more than one pain mechanism. Clinically, when neuropathic pain is diagnosed, consider other mechanisms if the pain lasts more than 3 months and consider appropriate individualized pharmacological treatments, including education and physical and psychological rehabilitation. Standard therapy with co-analgesics and adjuvants ± opioids should be considered. Ensure that non-pharmacological treatments and patient involvement in goal setting are part of the management plan. Be aware that perception and coping can affect how a patient responds to both the pain and the plan of action.

Neuropathic pain is challenging, but a stepwise careful approach can lead to significant benefits for patients. Appropriate individualized treatment for pain in high-risk individuals with substance use disorder can be beneficial to individual patients and the community.

References

1. **Brookoff D** (2000) Chronic pain: 1. A new disease? *Hosp Pract*, **35**(7), 45–59. https://bit.ly/37c0RV0
2. **Brookoff D** (2000) Chronic pain: 2. The case for opioids. *Hosp Pract*, **35**(9), 69–84. https://bit.ly/2OBGiuy
3. **Merskey H**, **Bogduk N** (1994) Part III: pain terms, a current list with definitions and notes on usage. In: Merskey H, Bogduk N (eds.) *Classification of Chronic Pain*, 2nd edn, IASP Task Force on Taxonomy, pp. 209–14. https://www.iasp-pain.org/Education/Content.aspx?itemNumber=1698
4. **Colloca L**, **Ludman T**, **Bouhassira D** *et al*. (2017) Neuropathic pain. *Nat Rev Dis Primers*, **3**, 17002. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5371025/pdf/nihms854102.pdf
5. **Dou Z**, **Yang L** (2019) The application of functional magnetic resonance imaging in neuropathic pain. https://www.intechopen.com/books/medical-imaging-principles-and-applications/the-application-of-functional-magnetic-resonance-imaging-in-neuropathic-pain (doi: 10.5772/intechopen.89200)
6. **Agency for Clinical Innovation**. *DN4 Assessment Tool*. https://www.aci.health.nsw.gov.au/__data/assets/pdf_file/0014/212900/DN4_Assessment_Tool.pdf
7. **Max MB, Lynch SA**, **Muir K**, **Shoaf SE**, **Smoller B**, **Dubner R** (1992) Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med*, **326**, 1250–6.
8. **Attal N**, **Cruccu G**, **Haanpaa M** *et al*.; **EFNS Task Force** (2006) EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol*, **13**, 1153–69.
9. **Saarto T**, **Wiffen PJ** (2007) Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*, **4**, CD005454.
10. **Finnerup NB**, **Otto M**, **McQuay HJ**, **Jensen TS**, **Sindrup SH** (2005) Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain*, **118**, 289–305.
11. **Gillman PK** (2007) Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol*, **151**, 737–48.
12. **Hagen N**, **Cantin L**, **Lapointe B** *et al*. (2017) Tetrodotoxin for moderate to severe cancer-related pain: a multicentre, randomized, double-blind, placebo-controlled, parallel-design trial. *Pain Res Manage*, **2017**, 7212713. https://doi.org/10.1155/2017/7212713
13. **Fornasari D** (2017) Pharmacotherapy for neuropathic pain: a review. Pain Ther, **6**(Suppl 1), S25–33. doi 10.1007/s40122-017-0091-4
14. **Moulin DE**, **Clark AJ**, **Gilron I** *et al*. (2007) Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage*, **12**(1), 13–21.
15. **Mu A**, **Weinberg E**, **Moulin DE**, **Clarke H** (2017) Pharmacological management of chronic neuropathic pain. *Can Fam Physician*, **63**, 844–52.
16. **Fisher K**, **Coderre T**, **Hagen N** (2000) Targeting N-methyl-D-aspartate receptor for chronic pain management: preclinical animal studies, recent clinical experience and future research directions. *J Pain Symptom Manage*, **20**(5), 358–73.
17. **Hagen N**, **Fisher K**, **Chary S** *et al*. (2007) An open-label, multi-dose efficacy and safety study of intramuscular tetrodotoxin in patients with severe cancer-related pain. *J Pain Symptom Manage*, **34**(2), 171–82. PMID: 17662911. doi:10.1016/j.jpainsymman.2006.11.008
18. **Zorina-Lichtenwalter K**, **Meloto CB**, **Khoury S**, **Diatchenko L** (2016) Genetic predictors of human chronic pain conditions. *Neuroscience*, **338**, 36–62. https://dx.doi.org/10.1016/j.neuroscience.2016.04.041
19. **aan het Rot M**, **Mathew SJ**, **Charney DS** (2009) Neurobiological mechanisms in major depressive disorder. *CMAJ*, **180**(3), 305–13.
20. **Bombay A** (2014) The intergenerational effects of Indian residential schools: implications for the concept of historical trauma. *Transcult Psychiatry*, **51**(3), 320–38.
21. **Goldberg JS** (2013) Chronic opioid therapy and opioid tolerance: a new hypothesis. *Pain Res Treat*, **2013**, 407504. https://doi.org/10.1155/2013/407504

22. **Arout CA**, **Edens E**, **Petrakis IL**, **Sofuoglu M** (2015) Targeting opioid-induced hyperalgesia in clinical treatment: neurobiological considerations. *CNS Drugs*, **29**, 465–86.
23. **Colvin LA**, **Bull F**, **Hales TG** (2019) Perioperative opioid analgesia—when is enough too much? A review of opioid induced tolerance and hyperalgesia. *Lancet*, **393**(10180), 1558–68.
24. **Lynch ME** (2005) A review of use of methadone for the treatment of chronic noncancer pain. *Pain Res Manage*, **10**(3), 133–44.
25. **Salpeter S**, **Buckley J**, **Bruera S** (2013) The use of very-low-dose methadone for palliative pain control and the prevention of opioid hyperalgesia. *J Palliat Med*, **16**(6), 616–22. https://doi.org/10.1089/jpm.2012.0612

Chapter 6

Dyspnoea and lung disease

Danielle Kain, Susan MacDonald, and Shalini Nayar

Attitude

To enable each learner to:

- Understand and appreciate the suffering associated with dyspnoea, and its profound impact on an individual's quality of life.
- Recognize that many conditions (other than lung disease) can produce dyspnoea.
- Recognize the unique trajectory pertaining to chronic lung diseases.
- Reflect on the significant symptom burden associated with chronic lung disease.
- Realize that chronic lung disease is often present with concomitant illnesses of other body systems.
- Understand the importance of early recognition and treatment of symptoms.

Skills

To enable each learner to:

- Integrate the key principles of history and physical examination into a management strategy for symptoms in chronic lung disease patients.
- Diagnose patients with urgent symptom needs.
- Diagnose the progression of disease into end-of-life care and its management for patients with lung disease.
- Identify the following clinical entities: chronic obstructive pulmonary disease (COPD), pulmonary embolus (PE), pleural effusion, superior vena cava syndrome, lymphangitic carcinomatosis, and idiopathic pulmonary fibrosis.
- Feel comfortable initiating opioid medications in the treatment of dyspnoea.

Knowledge

To enable each learner to:

- Describe the key factors in the pathophysiology of dyspnoea.
- Implement a diagnostic approach to shortness of breath.
- Recognize the scope of care in each setting for patients with chronic lung disease.
- Implement the appropriate treatment plan for patients in need, including pharmacologic and non-pharmacologic strategies.
- Describe the appropriate investigations and treatments based on aetiology.

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Dyspnoea

Case 6.1

G.F. is a 65-year-old male with a history of severe COPD [forced expiratory volume in 1 second (FEV1) = 36%] and remote myocardial infarction (MI). Ten years ago, he underwent a left pneumonectomy for non-small cell lung cancer (adenocarcinoma). At the time, he developed a PE and subsequent gastrointestinal bleed, so his anticoagulation was discontinued. He had ongoing pain over the left thoracotomy scar but otherwise did well. In the past 2 months, he has become progressively wheelchair-bound secondary to dyspnoea.

G.F. was last seen at the hospital 2 weeks ago with increased shortness of breath from baseline. He was treated for COPD exacerbation with a 1-week course of prednisone 50 mg per day and antibiotics for a week's duration. He initially felt better but has returned with worsening shortness of breath.

G.F. has asked about what he could do to improve his current symptom burden, namely dyspnoea and pain. He is unable to do his basic activities of daily living without significant help from his wife. He continues to smoke approximately one pack of cigarettes per day. He is uncertain if he qualifies for oxygen for home use because he is still smoking.

Question 1. What is dyspnoea?

There is no universally accepted definition of dyspnoea, but many agree with the American Thoracic Society who define dyspnoea as '… a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity'.[1] It is often used synonymously with the term breathlessness.

Dyspnoea is thought to have a number of different contributors, including physical, emotional, and psychological components.[2] 'For most patients, dyspn[o]ea begins with a *physiological impairment* that leads to stimulation of pulmonary and extrapulmonary afferent receptors'.[2] In other words, there is often a 'neuromechanical dissociation' which effectively results in a mismatch between the respiratory demand/load versus the ability to ventilate.[3] Some of these afferent messages trigger a response in the cortico-limbic areas of the brain, which are involved in the perception of threat and the experience of fear;[3] others stimulate the pulmonary stretch receptors, pulmonary C-fibres, and carotid body, among multiple other sites.[2] In advanced cancer, as well as in non-malignant life-limiting illnesses (such as COPD or congestive heart failure), the phenomenon of disease-related cachexia involves atrophy of the respiratory muscles, which, in turn, contributes to dyspnoea.[4]

Question 2. Can patients without lung disease have dyspnoea?

While common in lung disease, dyspnoea can be a symptom of many conditions and situations seen in palliative care. Patients who have circulatory issues that reduce the amount of oxygenated blood reaching the tissues may feel short of breath. Lack of oxygen-carrying cells (anaemia) can have the same result. Conditions that prevent expansion of the lungs (abdominal ascites or mass) can trigger feelings of breathlessness. Deconditioning can reduce exercise capacity and produce a sensation of shortness of breath with exertion. Before concluding the cause of dyspnoea, the astute clinician reviews the entire situation. What conditions does the patient have? What medications are they taking? What other bodily changes have occurred?. Even patients with respiratory conditions may have other reasons for feeling short of breath.

Table 6.1 The mMRC dyspnoea scale[5]

Grade	Description
1	Only troubled with strenuous exercise
2	Short of breath hurrying on level ground or a hill
3	Walks slower than others of the same age due to breathlessness on level ground
4	Stops due to breathlessness after 100 yards (90 m) or after a few minutes on level ground
5	Too breathless to leave the house or while dressing/undressing

Source: data from Munari, AB, et al. (2018) 'Modified Medical Research Council Dyspnea Scale in GOLD Classification Better Reflects Physical Activities of Daily Living'. *Respiratory Care*, Vol. 63, Issue 1, pp.77–85.

Question 3. What is the best way to initially approach dyspnoea?

The initial approach to dyspnoea is to focus on aetiologies based on history and physical examination and to treat and remove underlying causes, if possible and within the patient's goals of care. Is there increased dyspnoea *from baseline*, increased cough, or a change in sputum production or quality? Any recent travel or exposure to sick contacts? Is there another condition or diagnosis that is impacting his shortness of breath? Any haemoptysis or constitutional symptoms?

One way to quantify and standardize breathlessness is to use the modified Medical Research Council (mMRC) dyspnoea scale (see Table 6.1). The major purpose of this scale is to aid in quantification of the disability felt by a dyspnoeic individual.

G.F. is complaining of mMRC grade 5 dyspnoea. When prompted, he describes his dyspnoea on exertion as 'air hunger'. Several qualities of dyspnoea have been studied, with 'increased effort' as likely being secondary to a multitude of aetiologies, 'tightness' as strongly correlating with bronchoconstriction, and 'air hunger' as being associated with increased ventilatory demand. When further assessing the history in a dyspnoeic patient, one may find it easiest to follow a logical approach based on a head-to-toe assessment ('OPQRSTUV'), or body system aetiologies, or physiologic differential (see Box 6.1). Physiologically, dyspnoea can be differentiated by an increased respiratory drive versus impaired ventilatory mechanics.

In the case of dyspnoeic patients, especially in the context of chronicity as in G.F.'s case, a thorough physical examination from head to toe (to look for other possible causes of dyspnoea such as pallor from anaemia, for example), with particular focus on the cardiovascular system, is warranted. On physical examination, G.F. has typical features of COPD: a barrel chest and recruitment of his accessory muscles (sternocleidomastoid muscles and scalene muscles in his case), as well as a prolonged expiratory phase on auscultation and digital clubbing, but no cyanosis or pallor. Dyspnoea is a subjective experience, so patients who are hypoxaemic may not be dyspnoeic and dyspnoeic patients may not be hypoxaemic.

Question 4. Would further investigations be warranted in G.F.'s case?

G.F. had a chest X-ray consistent with COPD (see Figure 6.1), displaying hyperinflated lungs, with no evidence of overt consolidation. As he was no longer very ambulatory, had a previous history of pulmonary embolism (PE), and was very dyspnoeic, a computed tomography (CT) scan with

Box 6.1 OPQRSTUV assessment

- O: onset—when; identify triggers
- P: place(s)—on exertion or at rest?
- Q: quality—what does it feel like?
- R: relief—exacerbating or relieving factors
- S: severity—0–10, or verbal scale, faces, etc.
- T: timing—when started, daily pattern
- U: understanding shortness of breath and its impact
- V: values—patient's wishes and goals

Reproduced courtesy of Elizabeth Beddard-Huber, University of British Columbia, Vancouver, Canada.

contrast was done to rule out PE. It was negative for PE but showed a new 0.9-cm speculated nodule in the right lower lobe (RLL). Given his previous MI, a cardiac aetiology was also ruled out with measurements of his troponin I level and an electrocardiogram (ECG).

Question 5. What are the possible aetiologies of G.F.'s dyspnoea?

The most obvious answer is worsening of his known COPD related to his long-term smoking. From a pulmonary standpoint, there is no new acute illness. He has worsening pain. Dyspnoea is known to be multifactorial, with a complex interaction among physical factors, disability, mental health, and social/spiritual wellness (see Table 6.2).

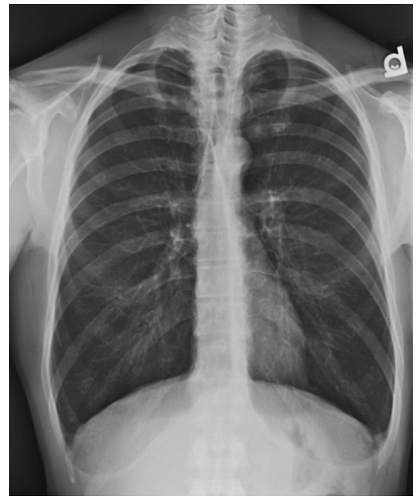


Fig. 6.1 Chest radiograph showing hyperinflation with COPD.
Reproduced courtesy of Dr. Brent Burbridge, University of Saskatchewan, Saskatoon, Canada.

Table 6.2 Aetiologies of dyspnoea

Malignant and associated conditions	Bronchial obstruction, superior vena cava syndrome, lymphangitic carcinomatosis, pleural effusion, pericardial effusion, pulmonary embolism, treatment-related pneumonitis
COPD-associated	Worsening FEV1, pulmonary hypertension, pneumonia, non-compliance with therapy, hypercapnic respiratory failure
Other	Cardiac causes (myocardial infarction, arrhythmia, congestive heart failure), neuromuscular disease, pain, intra-abdominal causes, acidosis, anaemia, deconditioning, panic attack

Other than smoking cessation, there are no known disease-modifying treatments to prevent the unrelenting course of COPD. Continued smoking denotes a faster progression of disease and a shorter lifespan. Treatments such as inhaler therapy are initiated to reduce exacerbation risk, enhance exercise capacity, and improve lung function (measured expiratory flow rates). Compliance needs to be ensured as a first step in these patients. This involves *watching* the patient use the inhaler and reiterating the importance of a full exhalation prior to using the device with a subsequent large inhalation of the medication, with a breath-hold of 6 seconds' duration. In the case of G.F., he was unable to breath-hold due to chronic thoracotomy scar pain and muscle weakness. Increases in his baseline pain medications were not tried for fear of worsening his breathing. Other considerations for his dyspnoea aetiology include psychological distress and the potential that he may have another malignancy.

Question 6. In general, what is COPD and how is it caused?

COPD is a progressive, incurable chronic lung disease, characterized by inflammation and airflow obstruction. Unlike in asthma, this obstruction is not entirely reversible. The most common cause of COPD is tobacco smoke, but recurrent exposure to inhaled pollutants (e.g. through occupational exposure to chemicals, fumes, and other irritants) can also cause COPD. Other less common aetiologies include genetic problems such as alpha-1-antitrypsin deficiency.[7]

Question 7. What test would you use to diagnose someone with COPD?

COPD is diagnosed with spirometry. A post-bronchodilator FEV1/forced vital capacity (FVC) ratio of less than 0.7 confirms the diagnosis.[8] The percentage predicted of FEV1 also provides important information with respect to staging the severity of COPD, as well as prognosis.

Question 8. What are the management goals in COPD?

The goals of therapy for COPD are to: (1) slow the progression of disease; (2) reduce the symptom burden associated with disease; (3) reduce exacerbations and hospitalizations; and (4) improve overall survival. These goals are achieved through a multifaceted approach, including smoking cessation, pharmacotherapy, non-pharmacologic interventions, surgical interventions, supplemental oxygen therapy, pulmonary rehabilitation (PR), education, and vaccination against respiratory infections.

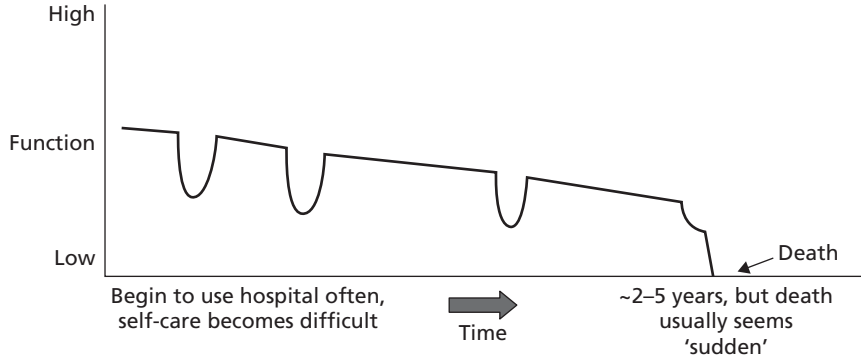


Fig. 6.2 Organ system failure trajectory.[9]
Adapted from Lunney J, Lynn J, Foley D *et al.* (2003) Patterns of functional decline at the end of life. *JAMA*, **289**, 2387–92.

Question 9. What is the expected disease trajectory of COPD?

COPD is the fourth leading cause of death in Canada and is among the highest per year hospital admission diagnoses. This is mainly due to the relapsing and remitting quality of the disease trajectory. There are some tools that are better able to prognosticate for patients with this disease, but it remains challenging. Patients may require high levels of intervention to maintain adequate ventilation and haemodynamic stability. Of the three major trajectories towards end of life, COPD most closely follows the organ system trajectory (see Figure 6.2).

In patients with the above trajectory, prognostication can be uncertain. Clearly, the functional reserve of a patient is diminished with each exacerbation, as can be seen by the decreasing baseline function. Prognostication in COPD has few validated scales. One such scale that can be useful is the Body mass index, Airflow obstruction, Dyspnoea, and Exercise capacity (BODE) Index (see Tables 6.3 and 6.4). As a patient loses weight due to respiratory cachexia and has worsening measured lung function, increased dyspnoea on the mMRC dyspnoea scale, and reduced exercise capacity, the score increases. A higher score denotes a shorter prognosis over a span of years. For every 1-point increase in the BODE score, there was a noted 34% increase in all-cause mortality, with a 62% increase in respiratory mortality noted in patients with COPD.

G.F. has a BODE score of 9, indicating the highest predicted mortality at 80% over 52 months. Most patients need a discussion early on in their illness trajectory regarding advance care planning

Table 6.3 BODE index

	Points on BODE			
	0	**1**	**2**	**3**
FEV1 (% predicted)	>65	50–64	36–49	<35
Distance walked in 6 minutes (m)	>350	250–349	150–249	<149
mMRC dyspnoea scale	0–1	2	3	4
Body mass index score	>21	<21	–	–

Adapted from Celli BR, Cote CG, Marin JM *et al.* (2004) The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in chronic obstructive pulmonary disease. *N Engl J Med*, **350**, 1005–12.

Table 6.4 Estimation of mortality using BODE index scoring[10]

Score	12-month mortality (%)	24-month mortality (%)	52-month mortality (%)
0–2	2	6	19
3–4	2	8	32
5–6	2	14	40
7–10	5	31	80

Adapted from Celli BR, Cote CG, Marin JM *et al.* (2004) The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in chronic obstructive pulmonary disease. *N Engl J Med*, **350**, 1005–12.

and expected transitions over time. COPD has its own particular challenges due to the high rates of hospitalizations. Often, patients are homebound with very severe symptoms as the disease progresses, and presentations become increasingly dramatic. Due to the constant cycling in and out of hospital, discussions regarding goals of care and future planning may not be fully addressed.

Question 10. What is the role of pulmonary rehabilitation in patients with COPD?

PR is an intensive, supervised exercise-based intervention, usually conducted in the outpatient setting over the course of 8–12 weeks, to help patients with their COPD symptoms. PR has been demonstrated to improve exercise tolerance, improve quality of life, and lessen dyspnoea.[11,12] There is also evidence to suggest that PR programme completion confers a survival benefit.[12]

Question 11. Would vaccinations be useful in this case?

Vaccinating patients with COPD against seasonal influenza and pneumonia can decrease the number of COPD exacerbations and hospitalizations for these individuals, decrease the incidence of community-acquired pneumonia, and improve all-cause mortality.[13,14]

Case 6.1 (continued)

G.F.'s only support is his wife. They have no family or friends close by to offer help. He has been relying on his wife to help him do all of his activities of daily living. She has also been going to work outside the home for 6 hours a day to reduce their financial strain.

Question 12. What other symptoms might accompany a diagnosis of COPD?

In studies focusing on health-related quality of life, patients with COPD have been shown to have reduced quality overall, as well as significant dyspnoea, pain, and high rates of mental health conditions (depression and anxiety). In one study, quality of life was lower than that of patients with non-small cell lung cancer. Patients often complain of social isolation, guilt, and physical frailty.[15] Added to this is the risk of a relentless progression of the disease and symptoms resistant to conventional therapies. Caregivers may experience compounded social isolation and burnout.[16]

At least eight major studies have focused on patient-reported symptoms and palliative care needs. Major areas of concern centre around a low level of social functioning, intense dyspnoea in

Table 6.5 GOLD criteria for treatment of COPD[6]

>2 moderate exacerbations OR >1 resulting in hospitalization	Group C LAMA	Group D LAMA or LAMA + LABA or ICS + LABA
0 or 1 moderate exacerbations not leading to admission	Group A Bronchodilator	Group B LAMA or LABA
	mMRC 0–1	mMRC >2

ICS, inhaled corticosteroid; LABA, long-acting bronchodilator; LAMA, long-acting muscarinic receptor antagonist.

Adapted from Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2020) *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2020 report.* https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_ WMV.pdf

the last year of life, and the perception of inadequate supports to care for their advanced disease in the home.[17,18]

Question 13. What management strategies can be employed to ease symptoms?

As previously discussed, the first step is to ensure maximized treatment with conventional therapies for advanced-stage COPD using the accepted Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (see Table 6.5). Compliance with these therapies is imperative. In addition, PR, as mentioned in Question 10, has been shown to be useful by having patients engage with each other, learn breathing techniques, and benefit their overall disease management (reduction in hospitalizations, improved function).

Current recommendations from the Canadian Thoracic Society suggest the initiation of dual therapy with a long-acting muscarinic antagonist (LAMA)/long-acting beta-agonist (LABA) for patients with moderate to severe COPD and/or an mMRC dyspnoea class of 2–4.[11]

Question 14. What non-pharmacologic options might you advise for relief of dyspnoea in patients, especially those with COPD?

There are several non-pharmacologic strategies that have evidence to support their effectiveness in the treatment of dyspnoea. These include temperature regulation to ensure a cool environment, use of a fan, and education regarding breathing techniques.[19,20] Exercise and strength training have been shown to reduce breathlessness in advanced lung disease in multiple studies, as has the use of mobility aids. The use of neuromuscular electrical stimulation (NMES) for those with advanced non-malignant and malignant disease who are *unable* to exercise has been reviewed recently by the Cochrane database, which found that NMES improved performances on the 6-minute walk test, as well as improved quadriceps muscle strength.[21]

Question 15. Are opioids used for the treatment of dyspnoea, and how might you initiate these in clinical practice?

Opioids remain the mainstay of treatment for dyspnoea in patients with palliative needs.[22] The Cochrane database includes the use of systemic opioids as a first-line addition to conventional treatments. They continue to be associated with positive outcomes when used in a safe, slow, and

judicious manner and do not result in increased carbon dioxide retention or respiratory depression.[23,24] There are several different ways of initiating opioids to help mitigate the symptom of dyspnoea.[25] The mechanisms by which opioids treat dyspnoea are not yet well understood. They decrease respiratory drive, decrease stimulation of the emotional areas in the brain triggered by dyspnoea (which results in a decrease in suffering), and suppress cough (which can trigger dyspnoea crises), and there may be an effect on the lung receptors themselves.[26] It is also postulated that they reduce medullary centre responses to changes in arterial oxygen and carbon dioxide levels, overall oxygen consumption, and preload, and have vasodilatory effects and global sedating effects.

Close medical follow-up and team support are imperative. Caregivers and patients must be able to follow a clear plan for initiation and titration of these medications when these medicines have been used with appropriate dosing and close supervision. Nebulized opiates have been studied numerous times and do not seem to confer any benefit with respect to side-effects or efficacy over systemic usage.

Case 6.1 (continued)

G.F. may well respond to an increase in his opioids for both his thoracotomy pain and his dyspnoea. G.F. needs to be reminded that his PRN or breakthrough doses of opioid can be used for dyspnoea and that he should keep track of the number of doses he requires daily in order to be more comfortable. This information will be useful to the clinician who will review it to determine whether the baseline dose should be increased.

Question 16. What non-opioid medications could be useful for G.F.?

In addition to opioids, several different classes of medications have been studied for the management of dyspnoea. A 2016 Cochrane review examining benzodiazepines did not demonstrate any improvement in breathlessness (for those with either COPD or malignancy) when used on their own.[27] Importantly, the use of these medications can also result in significant side-effects, including an increased risk of sedation, delirium, and falls risk.[27] Benzodiazepines could be considered as second or third line when opioids alone are not managing breathlessness *or* there is a significant anxiety component to a patient's symptomatology.

Emerging evidence is supportive of the use of medications that increase the circulating amount of the neurotransmitter serotonin, to take advantage of its potential role in the management of dyspnoea. Serotonin is involved in the regulation of respiratory physiology.[28] A randomized controlled trial examining the impact of sertraline [a selective serotonin reuptake inhibitor (SSRI)] on the reduction of breathlessness is currently under way in Australia,[28] and a recently published randomized feasibility study examining the effect of mirtazapine—a noradrenergic and specific serotonergic antidepressant—also demonstrated benefit in the management of dyspnoea.[29]

Question 17. What are the indications for oxygen therapy in COPD patients?

Oxygen therapy has long been known to have clear benefit for patients who are hypoxaemic at rest, demonstrating a survival benefit, as well as an improvement in patient-reported quality of life measures.[30] In those patients who are not hypoxaemic at rest, oxygen is only as effective as the use of a fan for symptom benefit. When oxygen 2 litres/minute via nasal prongs was compared to placebo in a randomized controlled trial, no significant symptom benefit was noted. Many clinicians will offer a trial of oxygen to see if the patient feels better. However, a Cochrane review from 2016 suggests that oxygen given *during exercise* for non-hypoxaemic patients can help to alleviate breathlessness.[31]

In order to qualify for long-term home oxygen therapy, patients must have a PaO_2 (partial pressure of oxygen) of <55 mmHg (can be <60 mmHg in the presence of certain comorbid conditions). In patients with mild or no resting hypoxaemia, there may be benefit for some patients when oxygen is given continuously on exertion.[24] In some places, PaO_2 values are not required if the patient is determined to have a prognosis of less than 3 months and require oxygen for palliation of symptoms.

Case 6.1 (continued)

G.F. was subsequently treated with low-dose hydromorphone on a PRN basis. He used hydromorphone 0.5 mg po q1h PRN, usually consuming approximately 4–5 mg of the medication in 24 hours. This worked very well initially for both pain and dyspnoea. With the reduction in pain, he felt better able to take in large breaths. He did well for a number of months. Unfortunately, he continued to decline with respect to symptoms and functionality. He was assessed and qualified for home oxygen. He eventually required a change in route of medication administration to parenteral hydromorphone (half of the equivalent oral dosage) to transition to end of life. He was able to have a comfortable home death with the involvement of a home palliative care team, consisting of a physician, nurse, care aides, and a social worker. Follow-up bereavement services were provided to his wife.

Question 18. What changes in management can we anticipate in end-of-life care?

Patients with end-stage lung disease may be unable to take oral medications due to dyspnoea as the disease progresses. Medications that are non-essential should be assessed for discontinuation. Opioids and other medications for symptom management should be continued and may require alternate formulation or change to a parenteral route that can be administered appropriate to the care setting (i.e. subcutaneous for community settings).[9] The frequency of breakthrough may be increased to q30 minute PRN if needed for symptom control.[32] There may be patients with such severe dyspnoea that they require admission to hospital or hospice to achieve symptom management.

Midazolam has been studied as an infusional agent that may benefit patients with severe dyspnoea that is uncontrolled by opioids alone (added to opioids). This combination has been shown to reduce severe dyspnoea. Care must be used and specialist palliative care consultation should be undertaken when it is considered.[32,33]

Within the last 48 hours of life, patients may also exhibit significant respiratory secretions. Patients treated with intravenous fluids or with a chest infection are at increased risk. Fluids or antibiotic therapies may need to be discontinued to attain symptom control. Treatment for secretions generally involves the addition of antimuscarinic anticholinergic agents such as scopolamine (0.2–0.6 mg subcutaneously q4–6h PRN; alternatively, a transdermal patch (1.5 mg/72 hours) or glycopyrrolate (0.1–0.4 mg subcutaneous q4–6h PRN).

Case 6.2

A.A. is a 72-year-old woman with a 75 pack-year smoking history. She lives in a single-level house with her husband who has advanced Parkinson's disease, and for whom she is the primary caregiver. She calls your clinic to book an urgent appointment.

Over the past few days, A.A. has become more short of breath, not relieved with her puffers or her morphine. She denies cough or change in sputum. She feels as though her 'heart is racing' but denies any other new symptoms. A.A. looks unwell. She has lost weight and is in moderate respiratory distress with a respiratory rate

of 28 and increased accessory muscle use. On chest examination, you note some dullness to percussion in the left lower lung field, decreased tactile fremitus, and decreased breath sounds at the left lung base. Her oxygen saturation is 83% on room air, and her heart rate is 121 bpm and regular. On examination of her extremities, you note that her right calf appears more swollen than her left, and it is slightly tender on palpation.

Chest X-ray reveals a left pleural effusion and a left hilar mass. An electrocardiogram (ECG) demonstrates a sinus tachycardia. A.A. is admitted to hospital for management of her hypoxia and dyspnoea, as well as an expedited work-up of her new left lung mass.

Question 19. In addition to a new pleural effusion and probable malignancy, what other diagnosis does A.A. likely have and what investigations would be needed to confirm the diagnosis?

A.A.'s clinical presentation is concerning for a deep vein thrombosis in the right leg that is causing a PE. The gold standard for diagnosis of a PE remains computed tomography pulmonary angiography (CTPA).[34] A ventilation–perfusion (VQ) scan is another option, though this has a lower sensitivity and specificity and is generally reserved for those who are unable to have CT.

Question 20. What is the 'classic' ECG finding for PE, and what are the most common ECG findings?

The classic finding accompanying a large PE seen on the ECG is the 'S1Q3T3' pattern—an S wave in lead I, and a Q wave and T wave inversion in lead III.[35] This pattern indicates right heart strain. The most common findings, however, are a new sinus tachycardia, and T wave inversion or flattening alone in lead III.[36] Even in the setting of the 'classic' finding as described above, a VQ scan, or preferably CTPA, is still required for definitive diagnosis. D-dimers are often not used due to lack of specificity of this test.

Question 21. What is the management of a PE?

Anticoagulation is the standard of care for the management of venous thromboembolic (VTE) disease, in both cancer and non-cancer patients. Previously, most patients with cancer-associated thrombosis were started on low-molecular-weight-heparin (LMWH) and would remain on this medication for at least 6 months.[37] Although most patients are *still* started and maintained on LMWH for at least 3 months, recent evidence points to transitioning these individuals to one of the novel oral anticoagulants (NOACs) for the duration of their treatment.[38] Rivaroxaban—a NOAC that inhibits factor Xa—is associated with less VTE recurrence in the cancer population and has about the same risk of bleeding as LMWH or warfarin.[38]

A.A. would likely remain on anticoagulation indefinitely because of her advanced disease, her poor prognosis, and the likelihood of VTE recurrence.

Question 22. What are the risk factors for the development of a PE, and which ones does A.A. have?

The major risk factors for VTE disease are described in Virchow's triad: stasis of blood flow, endothelial damage (i.e. injury to the blood vessel wall), and hypercoagulability.[39] A.A. unfortunately

has all of these risk factors—cigarette smoke is a well-known cause of endothelial damage; her dyspnoea significantly inhibits her ability to be active, thus resulting in stasis in blood flow,[40] and finally cancers—and lung cancer, in particular—produce a hypercoagulable state.[41]

Question 23. How would you diagnose a pleural effusion?

Most pleural effusions that cause symptoms (e.g. dyspnoea or chest pain) are large enough to been seen on a chest radiograph. Pleural effusions can also be diagnosed clinically, often presenting as A.A. did, with decreased breath sounds, dullness to percussion, and decreased tactile fremitus. If they are very large, effusions can result in asymmetric chest expansion, as well as mediastinal shift away from the side on which the effusion is located.

Question 24. What is the aetiology of pleural effusions?

Pleural effusions can be seen in a number of different medical conditions. Common non-malignant causes include pneumonia, heart failure, and renal problems. Malignant pleural effusions (MPEs) can be caused by nearly any malignancy, but the most common causes in men and women are lung and breast cancer, respectively.[42]

Question 25. What is the management of a malignant pleural effusion?

To diagnose a pleural effusion as malignant, a thoracentesis is necessary. Even in the setting of a known cancer diagnosis, up to 50% of pleural effusions can be non-malignant in their aetiology.[43] This matters because the management of an MPE differs from that of a benign pleural effusion. In addition to looking for malignant cells in the pleural fluid, tests are also done to check the pH and measure protein and lactate dehydrogenase levels, as well as cell count, culture, and sensitivity.

Depending on the amount of fluid removed, a thoracentesis can also be therapeutic and helpful in the management of dyspnoea. If the pleural effusion is recurrent, current guidelines would suggest the placement of an indwelling pleural catheter (IPC) or performing a talc pleurodesis (a procedure which introduces a sclerosing agent into the pleural space, causing the pleura to stick together, thus inhibiting the re-accumulation of fluid) to reduce symptoms and improve quality of life.[44,45]

MPEs do not always result in hypoxaemia, so it is more likely that the primary aetiology of AA's hypoxaemia is her PE.

Case 6.2 (continued)

A thoracentesis is performed, and 1.3 litres of pleural fluid are removed. A.A.'s dyspnoea improves, but unfortunately, cytology does reveal cancer cells. Further work-up reveals lytic lesions at T9 and L3, as well as hypodensities suspicious for metastatic disease in the liver. A biopsy of the hilar mass comes back as a poorly differentiated adenocarcinoma, and a formal diagnosis of stage IV non-small cell lung cancer is made. Medical oncology offered therapy, but on balance, A.A. felt she wanted her focus to be exclusively on quality of life and she declined systemic treatments.

A.A. is sent home with supplemental oxygen, anticoagulation, social work and nursing supports in place. Three weeks later (prior to her scheduled follow-up appointment with you), she phones you at your office in a panic—'I can't breathe! I feel like I'm being smothered!' You meet her in the emergency department. When you arrive, you see that she is in extreme respiratory distress. You note that she also has some new facial oedema, flushing, and distended neck veins.

Question 26. What is the clinical syndrome responsible for A.A.'s presentation and how is it diagnosed?

A.A. has symptoms consistent with superior vena cava (SVC) obstruction, a clinical syndrome where there is obstruction or compression of the SVC caused by mass effect in the thorax—either from the primary tumour itself, or metastatic disease in the thorax, and/or lymphadenopathy in the thorax.[46] Lung cancer is the most common cause for a malignancy-related SVC syndrome, followed by non-Hodgkin's lymphoma. The clinical presentation is characterized by dyspnoea, flushing in the face and neck, facial or periorbital oedema, increased venous markings in the upper chest and neck, and elevated jugular venous pressure (JVP).[46] SVC syndrome is diagnosed by CT scan of the thorax. Abnormalities can also sometimes be seen on a chest radiograph.

Question 27. What is the treatment for SVC syndrome?

The treatment for SVC syndrome can be multifaceted, and it depends on *when*, in the course of the disease, SVC obstruction occurs. Radiation therapy, chemotherapy, corticosteroids, and surgical stenting are all used in the management of this syndrome.[46] Stenting has become more commonplace in recent years and may be associated with increased survival.[47,48] Additional supportive care involves supplemental oxygen in hypoxaemic patients and elevation of the head of the bed.

Case 6.2 (continued)

In addition to seeing SVC obstruction and enlarging of the hilar mass, A.A.'s CT of the chest also revealed interlobar septal thickening, peribronchovascular thickening, and a new pleural effusion, this time on the right side.

Question 28. What diagnosis most likely represents these new radiologic findings?

These findings are most likely associated with lymphangitic carcinomatosis, which is an invasion and obstruction of the lymphatic vessels in the lung parenchyma by tumour cells. It can be caused by a number of different tumour types, including lung, gastrointestinal, and gynaecologic cancers.

Question 29. What is the clinical presentation of lymphangitic carcinomatosis?

The typical clinical presentation is dyspnoea (with worsening baseline dyspnoea if the patient already has some degree of breathlessness) and a dry cough. It is also often accompanied by hypoxaemia.

Question 30. What is the treatment of lymphangitic carcinomatosis?

Treatment is primarily supportive. Beyond treating the cancer itself with systemic therapy, there is very little treatment available for lymphangitic carcinomatosis. Many healthcare providers use corticosteroids, though there remains a dearth of evidence for this intervention.[49]

Question 31. What is A.A.'s prognosis, given these new clinical findings?

The prognosis of someone with lymphangitic carcinomatosis is quite poor, usually in the range of weeks to short months.

Case 6.2 (continued)

A.A. agrees to high-dose steroids for both her lymphangitic carcinomatosis, as well as her SVC, in an attempt to improve her dyspnoea. She agrees to see the radiation oncology service which recommends five fractions of palliative radiation for her SVC obstruction. Goals of care are revisited with the patient and her family, and she reaffirms that she wants only symptom-directed care. She requests transfer to the hospice and she spends a happy, comfortable week surrounded by friends and family. A.A.'s Palliative Performance Scale (PPS) then drops to 20%. Her morphine and other essential medications are changed to a subcutaneous route. Three days later, A.A. is having mouth care only and is unresponsive. She dies comfortably that evening, surrounded by her family.

Case 6.3

P.F. is a 55-year-old male with end-stage and severe idiopathic pulmonary fibrosis (IPF), living with the illness over the last 2 years. He has declined lung transplantation recently and came for a discussion regarding advanced management of his disease. He has tried both accepted treatments for IPF over the last 2 years and had significant progression on both treatments. The first was discontinued due to significant gastrointestinal side-effects. He remained on the second until very recently. The medication was discontinued at his request due to continued disease progression on treatment. His major complaints are of increased cough and oxygen requirements that are quickly becoming difficult to deliver. He has a home oxygen concentrator and remains on 10 litres/minute oxygen via nasal prongs. His family is incredibly supportive and includes his wife, two sons, and three grandchildren.

Question 32. What is the natural progression of IPF and what are the treatment options?

IPF is a chronic illness that follows the organ failure trajectory in its overall progression. The major mechanism of injury can be attributed mainly to lung fibroblast proliferation. Generally, disease may progress slowly at first but may quickly accelerate during periods of acute worsening or 'exacerbations'. Patients may be susceptible to other contributing illnesses such as pneumonia or PE, which *must be ruled out* during periods of acute worsening. Patients may be considered for lung transplantation and assessed early in the course of the illness, given the propensity to decline with severe morbidity. The median survival time is 2–5 years.

Disease progression may be manifested by increasing respiratory symptoms, worsening pulmonary function tests, progressive fibrosis seen on CT scans of the chest, or acute clinical respiratory decline (see Table 6.6).

Two medications are currently accepted as therapies for long-term management of IPF: pirfenidone (unknown mechanism) and nintedanib (tyrosine kinase inhibitor).[50] Each of these therapies is approved for patients with IPF and an FVC of 50–80%. Depending upon the individual patient's side-effect profile risk, either may be used. Studies comparing the two

Table 6.6 Factors associated with worsening IPF[1]

Baseline factors	Degree of dyspnoea DLCO <40% predicted on lung function Oxygen saturation <88% on walk test Extent of fibrosis on CT scan Right heart pressure
Longitudinal factors	Increasing dyspnoea Decrease in FVC >10% over time absolute value Decrease in DLCO >15% absolute value Worsening fibrosis on CT scan

DLCO, diffusion capacity of carbon monoxide; FVC, forced vital capacity.

Adapted from American Thoracic Society (1999) Dyspnea: mechanisms, assessment, and management. A consensus statement. *Am J Respir Crit Care Med*, **159**, 321–40.

medications show similar rates of discontinuation based on side-effects, including the major side-effect of gastrointestinal issues (nausea, vomiting, diarrhoea). The aim of treatment is to slow the rate of progression over time and both medications have been shown to do so with significance. Furthermore, studies have been done to compare these medications with respect to efficacy, with both being recognized as good therapeutic choices. Nonetheless, despite treatments, IPF is an overall progressive and morbid disease.

Question 33. What symptoms may progress in IPF patients?

Studies have been done at major IPF treatment centres, focusing on patient-reported qualitative data, as well as on reports by caregivers.[51] Patients complained commonly of feelings of frustration and anger regarding the diagnosis. In addition, they complained of intense dyspnoea, insomnia, cough, and familial strain. Caregivers felt unprepared for the disease trajectory and were frustrated with a perceived lack of supports or education for IPF. Patients, caregivers, and healthcare providers all felt a lack of confidence in the management of symptoms.

The burden of symptoms in patients with IPF is similar to that of COPD and other chronic lung diseases. A significant proportion of patients feel that their psychological needs are underestimated and undertreated. In one study, only 17/45 patients had access to palliative care services. In that same cohort, only 22 patients were prescribed opioids for dyspnoea or pain, and all felt benefit. Pain, although present to a large degree, was a largely unaddressed symptom in the majority of these studies.[52]

Question 34. What are future considerations for patients with chronic lung disease like IPF or COPD?

Future considerations would need to include a discussion of better documentation regarding advance care planning for all patients with chronic lung diseases. Specifically, when patients with IPF were retrospectively studied within the last year of life in one large study, most patients did not have clear documentation of their care wishes or a clear resuscitation status, even within the last 24 hours of life.[52] Those patients went on to have investigations such as CT scans or blood work within the last 24 hours of life. More than 80% of those patients reached the end of their lives in hospital, spending an average of 30 days in hospital within the last 6 months of life. There was very poor documentation regarding the place of death within the last year of life for all of them.[52]

Other considerations involve further work in streamlining prognostication to facilitate transitions to palliative community supports, if available.

Summary

There are many lung diseases that will require a palliative approach to care. Early involvement by palliative care can help mitigate the significant symptom burden and suffering that occur with chronic lung disease. Dyspnoea is one of the most distressing symptoms experienced in this patient population. Opioids can be helpful in relieving dyspnoea, along with many other pharmacological and non-pharmacological therapies. Clinicians should use standardized tools to assess prognosis and offer frank discussions around management. Long-term management of the lung condition is helpful in controlling symptoms and the palliative care clinician can play a key role.

References

1. American Thoracic Society (1999) Dyspnea: mechanisms, assessment, and management. A consensus statement. *Am J Respir Crit Care Med*, **159**, 321–40.
2. Parshall M, Schwartzstein R, Adams L *et al.* (2012) An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*, **185**(4), 435–52.
3. Lovell N, Wilcock A, Bajwah S *et al.* (2019) Mirtazapine for chronic breathlessness? A review of mechanistic insights and therapeutic potential. *Expert Rev Respir Med*, **13(2)**, 173–80.
4. Dudgeon D, Baracos VE (2016) Physiological and functional failure in chronic obstructive pulmonary disease, congestive heart failure and cancer: a debilitating intersection of sarcopenia, cachexia and breathlessness. *Curr Opin Support Palliat Care*, **10**(3), 236–41.
5. Munari, AB, Gulart AA, Dos Santos K, Venancio RS, Karloh M, Mayer AF (2018) Modified Medical Research Council Dyspnea Scale in GOLD classification better Reflects physical activities of daily living. *Respir Care*, **63**, 77–85.
6. Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2020) *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2020 report*. https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf
7. World Health Organization. https://www.who.int
8. Health Canada (2010) *Estimating the prevalence of COPD in Canada: reported diagnosis versus measured airflow obstruction*. Statistics Canada, Ottawa. https://www150.statcan.gc.ca/n1/pub/82-003-x/2014003/article/11908-eng.htm
9. Lunney J, Lynn J, Foley D *et al.* (2003) Patterns of functional decline at the end of life. *JAMA*, **289**, 2387–92.
10. Celli BR, Cote CG, Marin JM *et al.* (2004) The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in chronic obstructive pulmonary disease. *N Engl J Med*, **350**, 1005–12.
11. CTS position statement: Update in Pharmacotherapy for COPD. (2017) *Canadian Thoracic Society*.
12. Houchen-Wolloff L, Williams J, Green R *et al.* (2017) Survival following pulmonary rehabilitation in patients with COPD: the effect of program completion and change in the incremental shuttle walking test distance. *Int J Chron Obstruct Pulmon Dis*, **13**, 37–44.
13. Bekkat-Berkani R, Wilkinson T, Buchy P *et al.* (2017) Seasonal influenza vaccination in patients with COPD: a systematic literature review. *BMC Pulm Med*, **17**(1), 79.
14. Walters J, Tang J, Poole P *et al.* (2017) Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. *Cochrane Database Systematic Rev*, **1**, CD00139.
15. Gore JM, Brophy CJ, Greenstone MA (2000) How well do we care for patients with end stage chronic obstructive pulmonary disease COPD? A comparison of palliative care and quality of life in COPD and lung cancer. *Thorax*, **55**, 1000–6.
16. Edmonds P, Karlsen S, Khan S *et al.* (2001) A comparison of the palliative care needs of patients dying from chronic respiratory diseases and lung cancer. *Palliat Med*, **15**(4), 287–95.

17. Seamark DA, Blake SD, Seamark CJ *et al.* (2004) Living with severe chronic obstructive pulmonary disease (COPD): perceptions of patients and their carers. An interpretative phenomenological analysis. *J Palliat Med*, **18**, 619–25.
18. Curtis JR (2008) Palliative and end-of-life care for patients with severe COPD. *Eur Respir J*, **32**, 796–803.
19. Qian M, Politis J, Thompson M *et al.* (2018) Individualized breathlessness interventions may improve outcomes in patients with advanced COPD. *Respirology*, **23**(12), 1146–51.
20. Simon S, Weingärtner V, Higginson I *et al.* (2016) 'I Can Breathe Again!' Patient's self-management strategies for episodic breathlessness in advanced disease, derived from qualitative interviews. *J Pain Symptom Manage*, **52**(2), 228–34.
21. Jones S, Man WDC, Goa W *et al.* (2016) Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease *Cochrane Database Systematic Rev*, **10**, CD009419.
22. Kamal A, Maguire J, Wheeler J *et al.* (2012) Dyspnea review for the palliative care professional: treatment goals and therapeutic options. *J Palliat Med*, **15**, 106–14.
23. Smallwood N, Le B, Currow D *et al.* (2015) Management of refractory breathlessness with morphine in patients with chronic obstructive pulmonary disease. *Intern Med J*, **45**(9), 898–904.
24. Ansari AA, Pomerantz DH, Jayes RL *et al.* (2019) Promoting primary palliative care in severe chronic obstructive pulmonary disease: symptom management and preparedness planning. *J Palliat Care*, **34**(2), 85–91.
25. Rocker G, Horton R, Currow D (2009) Palliative of dyspnoea in advanced COPD: revisiting a role for opioids. *Thorax*, **64**(10), 910–15.
26. Mahler D, O'Donnell D (2015) Recent advances in dyspnea. *Chest*, **147**(1), 232–41.
27. Simon ST, Higginson IJ, Booth S *et al.* (2016) Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults *Cochrane Database Systematic Rev*, **10**, CD007354.
28. Watts GJ, Clark K, Agar M *et al.* (2016) Study protocol: a phase III randomised, double-blind, parallel arm, stratified, block randomised, placebo-controlled trial investigating the clinical effect and cost-effectiveness of sertraline for the palliative relief of breathlessness in people with chronic breathlessness. *BMJ Open*, **6**(11), e013177.
29. Higginson IJ, Wilcock A, Johnson MJ *et al.* (2020) Randomised, double-blind, multicentre, mixed-methods, dose-escalation feasibility trial of mirtazapine for better treatment of severe breathlessness in advanced lung disease (BETTER-B feasibility). *Thorax*, **75**(2), 176–9.
30. Nocturnal Oxygen Therapy Trial Group (1980) Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med*, **93**(3), 391–8.
31. Ekstrom M, Ahmadi Z, Bornefalk-Hermansson A *et al.* (2016) Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. *Cochrane Database Systematic Rev*, **11**, CD006429.
32. Masman AD, van Dijk M, Tibboel D, Baar FPM, Mathot RAA (2015) Medication use during end-of-life care in a palliative care centre. *Int J Clin Pharm*, **37**, 767–75.
33. Navigante AH, Cerchietti LCA, Castro MA, Lutteral MA, Cabalar ME (2006) Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. *J Pain Symptom Manage*, **31**, 38–47.
34. Moore A, Wachsmann J, Chamarthy M *et al.* (2018) Imaging of acute pulmonary embolism: an update. *Cardiovasc Diagn Ther*, **8**(3), 225–43.
35. Shopp J, Stewart L, Emmett T *et al.* (2015) Findings from a 12-lead electrocardiography that predict circulatory shock from pulmonary embolism: systematic review and meta-analysis. *Acad Emerg Med*, **22**(10), 1127–37.
36. Co I, Eilbert W, Chiganos T (2017) New electrocardiographic changes in patients diagnosed with pulmonary embolism. *J Emerg Med*, **52**(3), 280–5.

37. Khorana A, McCrae K, Milentijevic D *et al.* (2017) Current practice patterns and patient persistence with anticoagulant treatments for cancer-associated thrombosis. *Res Pract Thromb Haemost*, **1**(1), 14–22.
38. Streiff M, Milentijevic D, McCrae K *et al.* (2018) Effectiveness and safety of anticoagulants for the treatment of venous thromboembolism in patients with cancer. *Am J Hematol*, **93**(5), 664–71.
39. Anderson FA Jr, Spencer FA (2003) Risk factors for venous thromboembolism. *Circulation*, **107**(23 suppl 1), i9–16.
40. Tapson VF (2005) The role of smoking in coagulation and thromboembolism in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*, **2**(1), 71–7.
41. Schmaier A, Ambesh P, Campia U (2018) Venous thromboembolism and cancer. *Curr Cardiol Rep*, **20**(10), 89.
42. Roberts ME, Neville E, Berrisford RG *et al.* (2010) Management of a malignant pleural effusion: British Thoracic Society pleural disease guideline. *Thorax*, **65**, ii32–ii40.43. Heffner J, Klein J (2008) Recent advances in the diagnosis and management of malignant pleural effusions. *Mayo Clin Proc*, **83**(2), 235–50. doi: 10.4065/83.2.235
44. Davies H, Mishra E, Kahan B *et al.* (2012) Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion. *JAMA*, **307**, 2383–9.
45. Bibby AC, Dorn P, Psallidas I *et al.* (2018) ERS/EACTS statement on the management of malignant pleural effusions. *Eur Respir J*, **52**(1), pii: 1800349. doi: 10.1183/13993003.00329-2018
46. Wilson L, Detterbeck FC, Yahalom J (2007) Superior vena cava syndrome with malignant causes. *N Engl J Med*, **356**, 1862–9.
47. Rowell N, Gleeson F (2001) Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus. *Cochrane Database Syst Rev*, **4**, CD001316.
48. Nui S, Xu Y, Cheng L *et al.* (2017) Stent insertion for malignant superior vena cava syndrome: effectiveness and long-term outcome. *Radiol Med*, **122**(8), 633–8.
49. Hardy JR, Rees E, Ling J *et al.* (2001) A prospective survey of the use of dexamethasone on a palliative care unit. *Palliat Med*, 15(1), 3–8.
50. Rajala K, Lehto JT, Sutinen E *et al.* (2011) An Official ATS/ERS/JRS/ALAT Statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*, **183**, 788–824.
51. Bajwah S, Higginson IJ, Ross JR *et al.* (2012) Specialist palliative care is more than drugs: a retrospective study of ILD patients. *Lung*, **190**, 215–20.
52. Rajala K, Lehto JT, Saarinen M, Sutinen E, Saarto T, Myllarniemi M (2016) End-of-life care of patients with idiopathic pulmonary fibrosis. *BMC Palliat Care*, **15**(1), 85. https://doi.org/10.1186/s12904-016-0158-8

Chapter 7

Nausea and vomiting

Bernard J. Lapointe

Attitude

To enable each learner to:

- Realize the impact of nausea and vomiting on a patient's quality of life and daily care, as well as the potentially devastating effects on the family.
- Consider that the aim of treatment is the patient's comfort, and that this can be achieved even if full control of nausea and vomiting is not possible.
- Reflect on the complexity of the concerns that may face the patient with advanced illness, and the fact that nausea interrelates with other symptoms, emotions, and fears and cannot be dealt with in isolation.

Skills

To enable each learner to:

- Demonstrate a logical approach to identification of the specific causes of nausea and vomiting for each patient.
- Write a treatment plan for each patient, based on the specific triggers of nausea, the receptor(s) and neurotransmitter(s) involved, and the targeting antiemetic medications.
- Demonstrate a communication strategy for discussing the causes and treatment options with each patient and their family.

Knowledge

To enable each learner to:

- Summarize the pathophysiology of nausea and vomiting.
- Differentiate between the various groups of antiemetic medications and their indications, and also recall examples in each group, noting their main side-effects and contraindications.
- Discuss appropriate non-pharmacological modalities for the treatment of nausea and vomiting.

Case 7.1

C.M. is a 62-year-old woman who presents to her general practitioner with increasing pain in her left shoulder and left axilla. C.M. has detected swollen nodes in her axilla and she can feel a mass in the upper left quadrant of her breast. Her family physician, suspecting metastatic breast cancer, refers C.M. urgently to the breast centre of the nearest oncology department. A battery of diagnostic procedures, including imagery of her

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breast, chest, abdomen, and bones, is immediately ordered, as well as a needle biopsy of several lymph nodes. During this period, the pain reached an intensity of 5–7 on a visual analogue scale (VAS) and C.M. was prescribed a strong opioid long-acting hydromorphone at a dose of 3 mg po twice a day. After the first few doses, she developed nausea and vomiting, which she tried to control, without success, with leftover dimenhydrinate tablets. After a phone call with C.M., the family physician ascertains that C.M. does not show signs of opioid overdose. Her physician suspects that her nausea and vomiting are due to side-effects of the opioid. A dose of haloperidol 0.5 mg po three times a day is prescribed, to be taken regularly over the next few days and then taken on an as-needed basis.

Question 1. Why did C.M. develop nausea and vomiting, and how should you deal with these symptoms?

Nausea has been defined as 'an unpleasant painless subjective feeling that one will imminently vomit'.[1] It is often accompanied by autonomic symptoms such as pallor, cold sweat, salivation, tachycardia, and diarrhoea. Vomiting is a rapid, forceful evacuation of gastric contents from the stomach up to and out of the mouth. Nausea and vomiting are considered 'protective' mechanisms, warning of, and eventually evacuating, potentially toxic exogenous substances. Other related symptoms such as regurgitation, retching, and rumination (e.g. in the presence of a Zenker's diverticulum) need to be identified in the clinical investigation of the patient presenting with nausea and vomiting in order to select the best course of action.

We often think of nausea and vomiting as linked in a temporal continuum. However, nausea is frequently experienced without vomiting, and more rarely, vomiting can occur without preceding nausea. Nausea is more common and more disabling, feels worse, and lasts longer than vomiting.

There is a large list of usual causes of nausea and vomiting, which make a causal diagnosis challenging in everyday practice, including motion sickness, migraine headaches, medication use, ethanol abuse, infections of the gastrointestinal tract, and pregnancy, to name a few.

In patients with palliative care needs, these symptoms are more prevalent and result from a broad range of pathologic and physiologic conditions affecting the gastrointestinal tract, the peritoneal cavity, the central nervous system (CNS), and the endocrine and metabolic systems, and may also be the result of psychiatric conditions such as anxiety and depression.[2] Nausea and vomiting appear to increase in prevalence as the disease progresses. In patients admitted to specialist palliative care programmes, nausea has been reported by 36% of patients at the first contact with the service, 62% at 1–2 months before death, and 71% in the final week of life.[3,4,5]

Nausea and vomiting are also common in the palliative care context of patients with non-cancer diagnoses. The prevalence is up to 50% in non-malignant advanced disease such as heart failure (due to hyponatraemia, digoxin toxicity, or oedema of the gastrointestinal tract), chronic obstructive pulmonary disease (due to post-tussive vomiting, or side-effects of antibiotics or theophylline), and renal failure (due to uraemia, dialysis, or peritonitis).[6]

The mechanisms of the nausea/vomiting (emetic) pathways are complex and often difficult to elucidate. However, stimuli giving rise to nausea and emesis originate from visceral, vestibular, and chemoreceptor trigger zone (CTZ) inputs and are principally mediated by serotonin/dopamine and histamine/acetylcholine pathways. These pathways remain the basis for current pharmacological therapy of these symptoms.[7] See Box 7.1 for a list of the most common causes of nausea and vomiting in palliative care patients.

Box 7.1 Common causes of nausea and vomiting in palliative care patients

- Medication and toxic aetiology:
  - Opioids
  - Digoxin
  - Antibiotics/antiviral drugs
  - Cancer chemotherapy
  - Selective serotonin reuptake inhibitors (SSRIs)
- NSAIDs, ASA
- Anticonvulsants
- Theophylline
- Iron and potassium supplements
  - Idiosyncratic response (may occur with virtually any drug)
  - Ethanol intoxication
- Metabolic causes:
  - Renal or liver failure
  - Hypercalcaemia
  - Hyponatraemia
  - Diabetic ketoacidosis
  - Hyperthyroidism
- Pharyngeal and gastric irritation:
  - Oral/oesophageal candidiasis
  - Tenacious sputum/persistent cough
  - Peptic ulcer disease/gastritis
- Gastric stasis:
  - Opioids/anticholinergic drugs
  - Hepatomegaly/mechanical gastric outlet obstruction
  - Tumour ascites
  - Tumour infiltration
  - Autonomic dysfunction (may be associated with the anorexia–cachexia syndrome)
- Stretching/distortion of the gastrointestinal tract:
  - Constipation or faecal impaction (common in patients with advanced cancer or limited mobility, or receiving opioids)
  - Intestinal obstruction
  - Mesenteric metastasis

Box 7.1 *(continued)*

- Infections of the gastrointestinal tract:
  - Fungal, bacterial, and parasitic infections (common in immunosuppressed patients and in acquired immune deficiency syndrome/human immunodeficiency virus)
- Raised intracranial pressure:
  - Primary brain tumour/brain metastases
  - Cerebral infections
  - Tumour bleed
  - Meningeal infiltration
- Movement-induced:
  - Vestibular disorders (rare in advanced cancer)
  - Traction on tumour-involved mesenterium/viscera
- Psychosomatic (cortical) causes:
  - Anxiety/strong emotions
  - Strong odours or disturbing visual stimulus
  - Pain
  - Anticipatory nausea (occasionally in patients receiving chemotherapy)
- Radiation therapy
- Tumour-induced autonomic dysfunction

Question 2. How do you approach the patient with nausea and vomiting?

A careful history and physical examination will often contribute to the identification of the most likely cause of the symptoms, underlying mechanism(s), and neurotransmitter(s) involved. This allows for the identification of reversible causes and, consequently, the choice of antiemetic agents. In advanced cancer, gastric stasis and chemical disturbance are the most common causes of nausea and vomiting. However, it is important to recognize that 40–70% of cancer patients receiving opioids for pain control experience nausea and vomiting. Therefore, it is recommended that every patient receiving an opioid for the first time or undergoing a significant dose increase be prescribed an anti-nauseant. Note, however, that up to 25% of patients may have multiple causes for their nausea and vomiting.

It is also helpful to identify the duration of the symptoms in patients living with cancer:

- Acute: minutes or hours after administration of a treatment. If accompanied by troublesome symptoms, such as fever or severe pain, it will often need to be addressed as an emergency.
- Delayed: developing more than 24 hours after treatment.
- Chronic: not being linked to the treatment, but more to cancer spread or medication prescribed for pain or other chronic conditions.

Understanding of the 'emetic pathway' and the main neurotransmitters involved in this process may be helpful in choosing an antiemetic medication (see Figure 7.1). However, many antiemetics

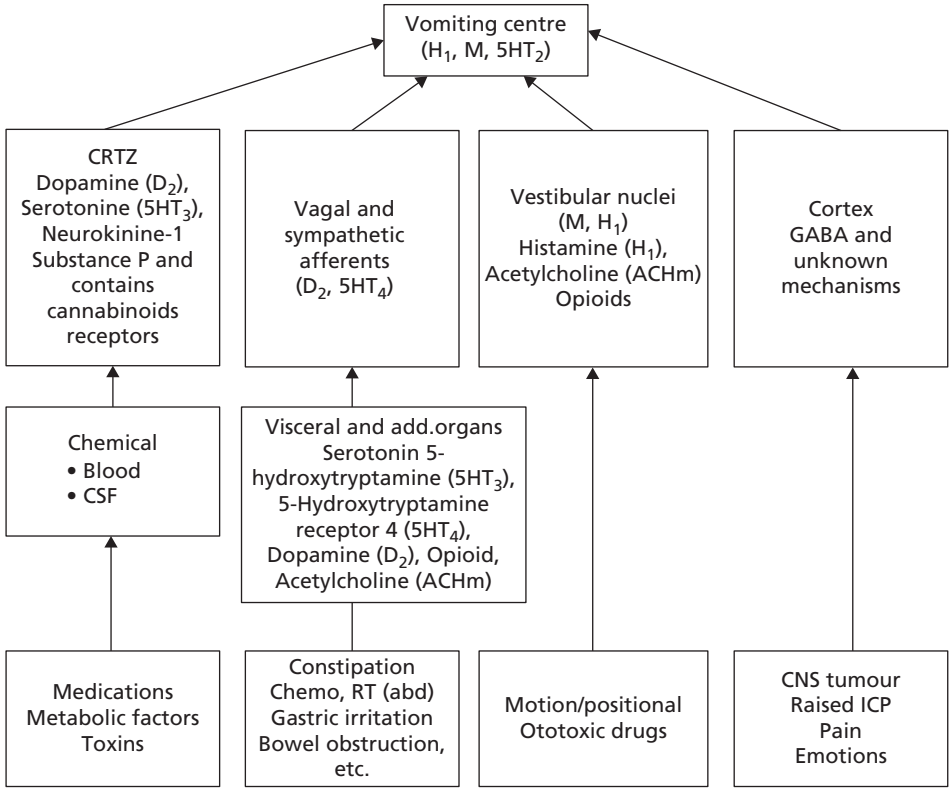


Fig. 7.1 Receptor pathways and neurotransmitters.
Source: data from Guide pratique des soins palliatifs (2019). 5th Edition, Regroupement de pharmaciens experts en soins palliatifs.(9)

have a broad spectrum of neurotransmitters blocking activity and work at multiple sites.[6] The selection of a route of absorption that will ensure drug bioavailability and efficacy is important as well. Oral administration will not be the preferred route in a patient with profuse vomiting. Parenteral administration is recommended if there is vomiting, severe gastric stasis, or gastrointestinal obstruction. Even in patients who are quite nauseated, but not vomiting, the parenteral route may be of benefit, at least until the nausea is under control.

If possible, determine if there is a single cause. In palliative care, many patients have multiple reasons to be nauseated, and extensive investigations to determine each of these may not be within the patient's goals of care. Consult the patient and determine both how much effort they are willing to expend to cope with the treatment or investigation of the underlying cause and the effect that their performance status may have. The extent of aggressiveness of treatment varies with the ability of the patient to cope. For example, patients with a PPS of 20% may not cope with extensive brain radiation for tumour mass effect, but a patient with a PPS of 60% may do well. Consider whether the causes of nausea are treatable (infection, hypercalcaemia, constipation) or likely not treatable (end-stage liver failure, end-stage renal failure). In discussion with the patient, determine what the goal of treatment is: complete reversibility of the underlying cause, reduction of the frequency of vomiting, reduction in the severity of nausea, etc. Ensuring that the patient and the clinician agree on how far/extensive the investigations and treatment are and what the desired

outcome is can be helpful when dealing with troublesome, and often challenging, symptoms such as nausea and vomiting. Consider whether correction of fluid, electrolyte, or nutritional deficiencies, either as a result of the disease or resulting from the emesis, is part of the overall goals of care. Automatically checking blood values can lead to unnecessary and unwanted treatment.

Reviewing the situation frequently is important. The clinical picture can change over the course of hours to days. A patient may seem to be stable but decompensate as the disease progresses. It is also important to frequently assess how well the treatment plan is working. As nausea is a miserable symptom to live with and it significantly reduces the patient's quality of life, it is in the patient's best interest to institute treatment and ensure follow-up is arranged.

The complex aetiology of nausea often requires a multimodal approach, using non-pharmacological approaches, dietary counselling, and careful prescription of drugs that may act on different receptors. Non-pharmacological treatments may include avoiding odours, opening windows for fresh air, ensuring toileting is not done at mealtimes, and changing position. Keeping the mouth clean is important—using rinses, toothbrushes, or a clean wet cloth to cleanse the mouth and reduce bad tastes. Avoiding heavy, fried, or spicy foods may be useful. Some patients find cold foods (popsicles) less emetogenic than hot or warm foods. Each patient is different—what works for one person may not work for another. Finding something that helps may be by trial and error.

Question 3. What medications can be helpful for C.M.?

The family physician of C.M. recognized that in patients living with cancer or other life-threatening illnesses, adverse medication reactions are among the most frequent causes of nausea and vomiting. This can occur even if the medication is taken at the prescribed dose. When nausea and vomiting occur as a result of the use of a medication, these symptoms are likely to present early in the course of its use. Opioids are often involved in the genesis of nausea and vomiting, as they frequently trigger the CTZ for emesis, which is located on the floor of the fourth ventricle and lies outside the blood–brain barrier. The CTZ is constantly in contact with the cerebrospinal fluid (CSF) and hosts receptors that will detect emetic toxins in both blood and the CSF. It then relays that information to the vomiting centre which is responsible for inducing the vomiting reflex. The CTZ is therefore believed to play an important protective function central to nausea and vomiting in the palliative care patient receiving medications presenting with metabolic disturbances or infections or receiving radiotherapy. Medications that can antagonize receptors found in the CTZ are dopamine (D2) antagonists such as butyrophenones, phenothiazines, or prokinetic agents, serotonin antagonists, and cannabinoids. Figure 7.1 documents the current understanding of the emetic pathways and Box 7.2 lists the most common antiemetic agents. These aim at helping the clinician select the most appropriate medication based on the mechanisms involved.

C.M. responded well to the regular administration of haloperidol at a low dose for a few days and now rarely experiences opioid-related nausea and vomiting. If you believe the aetiology to be opioid-induced nausea and vomiting, the medication can be titrated down and, if tolerated, discontinued after 7 days. In the absence of a favourable clinical effect, the treatment prescribed needs to be re-evaluated 48–72 hours after its initiation. If the response is partial, increase the dose of the initial agent, keeping in mind that higher doses may bring forward more side-effects. If there is little efficacy of the prescribed agent, explore other clinical conditions that may contribute to the symptoms. You may discontinue the initial agent and address the other potential causes (pathways) or use them in combination. For example, because C.M. is receiving a strong opioid, constipation and/or delayed gastric emptying (which are common side-effects of opioids) may contribute to, or cause, her nausea and vomiting. C.M. would then benefit from a prescription of oral laxatives and a motility agent (either metoclopramide or domperidone). Infrequently,

Box 7.2 Antiemetic medications

- Prokinetic agent (a D2 receptor blocker that acts centrally and peripherally):
  - Domperidone: fewer CNS side-effects.
  - Metoclopramide: potential for extra-pyramidal reaction and somnolence.
- Dopamine receptor antagonists:
  - Phenothiazines (e.g. methotrimeprazine and prochlorperazine) are less used today than haloperidol and olanzapine. They need to be carefully monitored in the elderly and may cause hypotension, and methotrimeprazine may cause significant sedation.
  - Other antipsychotic agents (haloperidol and olanzapine). As mentioned previously, haloperidol, because of its powerful and specific blocking of D2 receptors, its low potential for sedation, and its long duration of action, is often considered as a first-line agent for CTZ-mediated nausea and vomiting. Olanzapine is an atypical antipsychotic with high affinity for multiple dopamine, serotonin, H1, and cholinergic receptors. It has been used increasingly in palliative care in cases that are refractory to other agents. Dose recommendations are 2.5–10 mg per day (at night-time preferably). It causes fewer extra-pyramidal symptoms but will cause somnolence.
- Selective $5HT_3$ receptor antagonists act on $5HT_3$ receptors found in the CTZ and gastrointestinal tract. Examples are granisetron, ondansetron, and palonosetron. Primarily used for chemotherapy-induced emesis and tend to have more limited use in palliative care.
- Neurokinin (NK)-1 receptor antagonists (aprepitant, fosaprepitant, casopitant, rolapitant). Efficacy in preventing and treating chemotherapy-induced nausea and vomiting, nausea in the presence of gastrointestinal obstruction, and other refractory nausea.
- Other agents:
  - Cannabinoids. There is evidence of the efficacy of cannabinoids in chemotherapy-induced nausea/vomiting and anorexia–cachexia syndrome. Also have an anxiolytic effect. It is recommended to start treatment at a very low dose and to increase slowly using an oral preparation. The presumed mechanism of action is related to suppression of intestinal motility via CB1 receptors, at the level of the CTZ. Nabilone, a synthetic cannabinoid, may also manipulate $5HT_3$ and D2 receptors.
  - Corticosteroids. Dexamethasone is a useful prophylactic antiemetic for patients receiving certain types of chemotherapy and who experience acute or delayed nausea and vomiting. Long-term use of corticosteroids has potentially undesirable side-effects. Dexamethasone is also very helpful in the management of vomiting secondary to increased intracranial pressure.
  - Benzodiazepines. Lorazepam, midazolam, clonazepam, and alprazolam may be useful for the management of anticipatory nausea and vomiting and in combination with another anti-nauseants when anxiety is severe and contributes to the severity of the symptom.
  - Antihistaminic agents (H1 receptor antagonists with a potential action on antimuscarinic activity). Dimenhydrinate, diphenhydramine, hydroxyzine, promethazine. Act via a

Box 7.2 *(continued)*

vestibular mechanism and on the vomiting centre. They have been used in motion-induced sickness but may be useful in raised intracranial pressure.

Sources: data from:

- Glare P., Miller J. Nikolova T., Tickoo, R. Treating nausea and vomiting in palliative care: a review. Clin Interven Aging 2011: 6: 243–259.[6]
- Regroupement de pharmaciens experts en soins palliatifs. Association des pharmaciens des établissements de santé du Québec. Guide pratique des soins palliatifs (2019). 5th Edition.[9]
- Ware MA, Daeninck P, Maida V. A review of nabilone in the treatment of chemotherapy-induced nausea and vomiting. Ther Clin Risk Manag 2008;4(1): 99–107.[10]
- Passik SD, Lundberg J, Kirsh KL, et al. A pilot exploration of the antiemetic activity of olanzapine for the relief of nausea and vomiting in patients with advanced cancer and pain. J Pain Symptom Manage. 2002; 23(6): 526-532.[11]
- Hendren G, Aponte-Feliciano A, Kovac A. Safety and efficacy of commonly used antiemetics. Expert Opin. Drug Metab. Toxicol. (2015) 11(11) p1753–1767.[12]

refractory nausea and vomiting may need to be addressed with a combination of agents or agents that have a broad range of effects on multiple pathways (see Figure 7.1 and Box 7.2). In the case of a refractory syndrome, corticosteroids may offer some benefit, but we always have to evaluate the potential side-effects of these drugs. Combinations of agents carry a higher risk of undesirable side-effects.

Case 7.1 (continued)

C.M. is now anxiously awaiting the results of the various investigations, including the pathological diagnosis of her suspicious masses. Her oncologist meets with her and her life partner a few days later and shares the following results. C.M. is presenting with a stage III breast tumour which has spread to some axillary lymph nodes. The tumour is HER2+, ER–, and PR–. In discussion with C.M., the oncologist recommends a neo-adjuvant course of chemotherapy to shrink the tumour prior to surgery. C.M. receives four cycles of AC (adriamycin/cyclophosphamide) chemotherapy, during which she experiences moderate to intense nausea, vomiting, and some mouth sores. She becomes very anxious and states that the symptoms are so disabling that she is questioning the value of continuing with the proposed chemotherapeutic treatment. Her oncologist then prescribes a combination of agents, adding the $5HT_3$ antagonist dexamethasone to the D2 antagonist haloperidol. This combination allows for the completion of the course of AC and the completion of four cycles of AC. C.M. then starts a 3-month course of taxol-herceptin (paclitaxel/trastuzumab).

Question 4. How common is nausea and vomiting in cancer patients? What are the causes?

Nausea and vomiting represent two of the most distressing side-effects of cancer treatment. These symptoms can occur in up to 80% of patients and have a significant impact on the patient's quality of life, for example in inducing metabolic imbalance, nutritional depletion, and anorexia, leading to deterioration of the patient's physical and mental status.[13]

Chemotherapy-induced nausea and vomiting

The incidence of acute (within 24 hours of treatment) and delayed (occurring more than 24 hours after treatment) chemotherapy-induced nausea and vomiting varies from patient to patient and the emetogenic potential of the specific drugs chosen. The emetogenic potential may increase in relation to the dose prescribed or as a result of the use of one agent in combination with another. However, in recent years, many new antiemetics and antiemetic combinations have been shown to decrease the intensity of this complication of cancer treatments.

C.M. has been developing severe nausea and vomiting while receiving two drugs (paclitaxel/trastuzumab) with minimal or low risk for emesis. Pre-chemotherapy prevention recommendations are based on the emetogenic potential of the selected drugs and, in the case of drugs with minimal risk for emesis, the intensity of the symptoms experienced by the patient.

Guidelines for the prevention of nausea and vomiting during the treatment of cancer can be found on the National Comprehensive Cancer Network.[14]

Radiation-induced nausea and vomiting (RINV)

Radiation therapy is an important cause of treatment-induced nausea and vomiting. Some studies suggest an up to 80% incidence rate of these symptoms in patients receiving radiotherapy.[15] For patients at high risk of developing RINV, most guidelines recommend a prophylaxis with a $5HT_3$ receptor antagonist. Based on the response, dexamethasone can be added.[13]

Anticipatory nausea and vomiting (ANV)

ANV is probably a respondent conditioning (Pavlovian) response that usually happens after few courses of a specific treatment. Classically, the patient will experience nausea and vomiting before the next treatment will begin. Nausea and vomiting may happen at home before leaving for the treatment centre or when arriving in the oncology treatment centre, possibly the result of triggers such as smells, sounds, or sights.

The usual approach for this syndrome is non-pharmacologic. Relaxation techniques, including guided imagery, hypnosis, and distraction, can be offered. In some studies, benzodiazepines have shown some benefit. The best way to avoid ANV is to identify the emetic potential of the therapy offered and to prescribe prophylaxis to avoid the intense symptoms.

Case 7.1 (continued)

After completion of the neo-adjuvant therapy, the oncologic and surgical team reviewed the new diagnostic imagery tests and were very satisfied with the clinical response experienced by C.M. They proposed that she underwent a partial mastectomy with sentinel node biopsy. After surgery, C.M. is prescribed trastuzumab every 3 weeks and underwent adjuvant radiotherapy. She completed a total of 1 year of trastuzumab.

Unfortunately, 11 months later, C.M. starts complaining of abdominal bloating and pain, loss of appetite, and postprandial vomiting. She is now using more opioids to control her abdominal pain. She is found to have developed numerous liver, peritoneal, and retroperitoneal metastases and ascites. The physical examination reveals a significant hepatomegaly and a large volume of ascites. When further questioned, C.M. explains that she usually has some appetite in the morning but feels that over the day, most of the food ingested is staying in her stomach. She often will vomit in the afternoon and feels better after this. She also reports that she is constipated and since she has difficulty ingesting liquids, she is not using the laxatives previously prescribed.

Question 5. What is happening and how can you manage this new syndrome?

Many factors are contributing to the development of this new syndrome of abdominal discomfort, anorexia, and late vomiting. In the presence of significant hepatomegaly, ascites, peritoneal/retroperitoneal metastases, constipation, and increasing use of opioids, a significant delay in gastric emptying, and slowed peristaltic activity are suspected. Mechanical obstruction needs to be ruled out. The recent radiological investigations show no gastrointestinal obstruction but does document distension of the gastric cavity, a large amount of constipation, and ascites. C.M. is admitted on the family medicine ward, and corticosteroid therapy (dexamethasone) is initiated immediately to decrease peri-tumoral inflammation and oedema causing hepatic distension and pain. The chronic constipation is treated using suppositories and enemas, followed by maintenance oral laxatives. C.M. is referred to the interventional radiologist for an ascites tap to drain her ascites and you also prescribe her a motility agent (metoclopramide or domperidone) that will help relieve some of the gastric stasis symptoms (anorexia and late vomiting).

Case 7.1 (continued)

Her discomfort rapidly abates and she is able to return home with the medication prescribed during her hospitalization. Before she is discharged home, you take the time to review with her some non-pharmacological approaches that could help her better manage her anorexia, as well as the symptoms of nausea and vomiting.[6]

Question 6. What are non-pharmacological approaches for management of nausea and vomiting?

Similar to how you would counsel on the approach to managing any symptom, it is important to explain the current situation, provide information, and answer all your patient's questions.

The smell of certain foods or perfume can trigger nausea. Your patient may want to try eating in a different room than the one where the food was prepared. Encourage taking small quantities of food on a more frequent basis, and frequent small volumes of liquids to maintain hydration. Fatty, spicy, and highly salty food must be avoided, unless the patient has a strong craving for them. Good oral hygiene is paramount, and you need to monitor for the possible development of oral candidiasis.

Post-meals, encourage walking small distances and sitting upright. Do not lie down immediately after eating. Consider ginger. Various preclinical and clinical studies have suggested ginger as a potentially helpful and safe treatment for nausea and vomiting in the context of pregnancy and as an adjuvant treatment for chemotherapy-induced nausea and vomiting, but we are lacking evidence in the context of advanced disease.[16] Relaxation techniques, cognitive behavioural therapy, massage, acupuncture, or acupressure may be helpful for certain patients.[17]

Conclusion

Nausea and vomiting are frequently experienced by patients living with a life-threatening illness. Nausea and vomiting can be very debilitating/disabling and may have a profound negative impact on the quality of life of our patients. It is essential for every physician to take these symptoms seriously and treat them rapidly and appropriately.

References

1. **Hasler W**, **Chey W** (2003) Nausea and vomiting. *Gastroenterology*, **125**, 1860–7.
2. **Quigley EM**, **Hasler WL**, **Parkman HP** (2001) AGA technical review on nausea and vomiting. *Gastroenterology*, **120**, 263–86.
3. **Donnelly S**, **Walsh D** (1995) The symptoms of advanced cancer: identification of clinical and research priorities by assessment of prevalence and severity. *J Palliat Care*, **11**(l), 27–32.
4. **Vainio A**, **Auvinen A** (1996) Prevalence of symptoms among patients with advanced cancer: an international collaborative study. **Symptom Prevalence Group.** *J Pain Symptom Manage*, **12**(1), 3–10.
5. **Fainsiger R.**, **Miller MJ**, **Bruera E** *et al.* (1991) Symptom control during the last week of life on a palliative care unit. *J Palliat Care*, **7**(1), 5–11.
6. **Glare P**, **Miller J, Nikolova T**, **Tickoo R** (2011) Treating nausea and vomiting in palliative care: a review. *Clin Interven Aging*, **6**, 243–59.
7. **Kuo B**, **Singh P**, **Yoon S** (2016) Nausea: a review of pathophysiology and therapeutics. *Ther Adv Gastroenterol*, **9**, 98–112.
8. **De Kock I** (2012). Nausea and vomiting. In: Oneschuk D, Hagen N, MacDonald N (eds.) *Palliative Medicine: A Case-Based Manual*, 3rd edn, pp. 136–148. Oxford University Press, Oxford.
9. **Regroupement de pharmaciens experts en soins palliatifs** (2019) *Guide Pratique des Soins Palliatifs*, 5th edn. Association des pharmaciens des établissements de santé du Québec, Québec.
10. **Ware MA**, **Daeninck P**, **Maida V** (2008) A review of nabilone in the treatment of chemotherapy-induced nausea and vomiting. *Ther Clin Risk Manag*, **4**(1), 99–107.
11. **Passik SD**, **Lundberg J**, **Kirsh KL** *et al.* (2002) A pilot exploration of the antiemetic activity of olanzapine for the relief of nausea and vomiting in patients with advanced cancer and pain. *J Pain Symptom Manage*, **23**(6), 526–32.
12. **Hendren G**, **Aponte-Feliciano A**, **Kovac A** (2015) Safety and efficacy of commonly used antiemetics. *Expert Opin Drug Metab Toxicol*, **11**(11), 1753–67.
13. **PDQ Supportive and Palliative Editorial Board** (2018) *Treatment-Related Nausea and Vomiting*. https://www.cancer.gov/about-cancer/treatment/side-effects/nausea/nausea-hp-pdq
14. **National Comprehensive Cancer Network.** *NCCN Clinical Practice Guidelines in Oncology: antiemesis*. https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf
15. **Dennis K**, **Maranzano E**, **De Angelis C** *et al.* (2011) Radiotherapy-induced nausea and vomiting. *Expert Rev Pharmacoecon Outcomes Res*, **11**(6), 685–92.
16. **Bodagh MN**, **Maleki I**, **Hekmatdoost A** (2018) Ginger in gastrointestinal disorders: a systematic review of clinical trials. *Food Sci Nutr*, **7**(1), 96–108.
17. **Pan CX**, **Morrison RS**, **Ness J** *et al.* (2000) Complementary and alternative medicine in the management of pain, dyspnea and nausea and vomiting near the end of life. A systematic review. *J Pain Symptom Manage*, **23**(3), 237–43.

Chapter 8

Constipation

Tim Hiebert and Stefan Riel

Attitude

To enable each learner to:

- Recognize that constipation is a common and significant source of discomfort affecting quality of life in patients with terminal illness.
- Recognize the importance of ongoing assessment of bowel function.
- Adopt the habit of routinely prescribing laxatives to patients receiving opioids.

Skills

To enable each learner to:

- Obtain an appropriate history and physical examination in order to diagnose constipation.
- Identify and address underlying causes of constipation.
- Classify commonly used therapies for constipation, including osmotic laxatives, stimulant laxatives, and other agents that promote bowel motility.
- Develop a comprehensive approach to patients with constipation, including assessment, investigations, and treatment.
- Describe an approach to treating opioid-induced constipation (OIC).

Knowledge

To enable each learner to:

- Understand the pathophysiology of altered bowel motility, emphasizing the effects of drugs on the bowel and the presence of an altered state of motility in patients with advanced illness.
- Be aware of the signs and symptoms of severe constipation and faecal impaction versus bowel obstruction.
- Understand the mechanisms underlying OIC.

Case 8.1

D.C., a 76-year-old widow with osteoarthritis, carcinoma of the breast, and cutaneous metastases to the chest wall, presents to the emergency department, complaining of increasing pain and foul-smelling discharge from an open skin lesion. She has been taking acetaminophen/codeine tablets (325/8 mg) and ibuprofen, to poor effect. Her appetite is good; her bowel movements occur two to three times per week and are hard in consistency. This has been her pattern for 3 or 4 years. Other medications include daily docusate and psyllium fibre.

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The emergency medical officer diagnoses a soft tissue infection, prescribes a course of oral ciprofloxacin, and initiates oral morphine 5 mg every 4 hours, to good effect. D.C. is sent home on long-acting morphine 15 mg twice a day and 2.5 mg every 4 hours, as needed, with instructions to follow up with her family doctor.

Question 1. Discuss the risk factors for constipation. Does Mrs D.C. have chronic constipation?

Constipation is frequent in the elderly, those with chronic illnesses, and patients with nearly any advanced illness. It is defined functionally as difficult passage of hard and/or infrequent stools, or a decrease in stooling frequency to twice or less per week. The Rome IV criteria for constipation provide detailed criteria for the diagnosis of constipation in various circumstances.[1] Factors which predispose to constipation include:

- Diet poor in fluid or bulk.
- Malnutrition.
- Immobility.
- Environmental factors (change of setting, lack of privacy, inconvenient facilities).
- Medications—diuretics, chemotherapeutics, opioids, sedatives, antipsychotics, anticholinergics, tricyclic antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), antihistamines, phenothiazines, iron, and serotonin antagonists.
- Metabolic disorders such as hypothyroidism, uraemia.
- Electrolyte disturbances (hypercalcaemia, hypo-/hypernatraemia).
- Direct malignancy effects or other anatomic abnormalities.
- Neurologic disorders (cord compression, autonomic dysfunction).
- Age over 65.

D.C. does have long-standing mild chronic constipation. Her age, immobility, and use of ibuprofen and codeine are all contributing factors. Low-grade or chronic constipation can be easy to overlook, however, so the diagnosis of constipation requires a high index of suspicion. An accurate history, detailing medications, laxative use, stool frequency and consistency, diet, mobility, and associated symptoms should be obtained, especially prior to starting or increasing opioid analgesia.

Question 2. What is the pathophysiology underlying constipation in patients with advanced illness?

Normal bowel function requires coordination of gut motility, molecular transport across the bowel wall, and reflexes of defecation. Motility is mediated by the autonomic nervous systems, as well as by hormones active in the gut. Adrenergic, muscarinic, dopaminergic, serotonergic, and opioid receptors all influence gut motility. Fluid and electrolyte transport across mucosal surfaces is a complex phenomenon with incomplete understanding.[2] We know that opioids slow intestinal transit in both the small and large intestines, resulting in increased fluid absorption. Moreover, opioids increase rectal sphincter tone and reduce awareness of rectal filling. Laxative therapies will usually combine laxatives which maintain hydration of bowel contents (osmotic laxatives) with those stimulating bowel transit (stimulant laxatives).

Case 8.1 (continued)

D.C. reports that she has not moved her bowels for 5 days and now complains of mildly decreased appetite and abdominal bloating. Her physician, having read the emergency department report from the previous week, realizes that D.C. was not prescribed a laxative with her opioid increase and initiates one to two senna tablets (elemental sennosides—8.6 mg per tablet) daily as needed. No further follow-up is arranged.

Question 3. Do you think these laxative choices and doses are appropriate?

Unless contraindicated, *all* patients should receive prophylactic laxatives while on opioids. As needed, or PRN, laxatives are likely to cause fluctuations between hard, infrequent stools and uncontrolled loose bowel movements, causing discomfort and frustration and might even contribute to poor adherence to treatment. Instead, laxatives should be regularly scheduled and titrated to response. In rare cases of normal bowel function despite opioids, laxatives can be decreased to PRN or discontinued.

Evidence for the management of constipation in palliative care is limited,[3] and practice is generally guided by combining the available evidence with expert opinion.[4,5] Treatment choices should consider the severity of a patient's symptoms, performance status, and individual preferences. Canadian consensus recommendations endorse the use of stimulant laxatives alone or in combination with osmotic laxatives.[4] The European consensus group suggest osmotic laxatives in combination with a stimulant as first line.[5] For D.C., a combination of both a stimulant (senna) and an osmotic laxative [polyethylene glycol (PEG)] would be more effective than her current regimen of senna, docusate, and psyllium fibre. Stool softeners are usually not sufficient to treat constipation in advanced illness[6] and daily psyllium fibre is not recommended for D.C. because her fluid intake has declined. Dietary fibre can contribute to constipation if there is insufficient fluid intake (>1.5 litres/day).

Prevention of constipation should be the primary goal. Adequate fluid intake, together with physical activity as able, should be encouraged together with laxatives for primary or secondary prevention.

Case 8.1 (continued)

D.C's infection has resolved; her pain is relieved, and morphine is successfully discontinued. Over several months, she develops episodic constipation, despite taking senna two tablets and PEG 17 g twice a day. Her weight and appetite are decreasing, as is her fluid intake. The onset of new mid-back pain leads to the initiation of long-acting morphine in place of maximal doses of acetaminophen/codeine. Pain control is improved, but bowel function worsens and soon she begins to complain of nausea and reports soiling herself with liquid stool. She goes to a community clinic and is advised that she has 'a touch of flu'.

Question 4. How would you conduct an assessment for constipation (history and physical)?

As always, a thorough history followed by appropriate physical exam and rational investigations are essential.

History

- Bowel history:
  - Inquiry into the pattern of movements, past and present, the quantity and consistency of stool, difficulties during defecation (pain from hard stools, burning due to loose stools, a sense of incomplete evacuation), passing of flatus, and the patient's historically 'normal' pattern. Lack of flatus is concerning for obstruction or ileus, rather than simple constipation (see Chapter 9). Typically, bowel patterns range from once every 3 days to as many as three times a day. Changes in stool consistency, appearance, odour (maroon or black, tarry, and foul-smelling stools may indicate a gastrointestinal bleed).
  - The Bowel Performance Scale is a validated tool that can be useful in managing constipation.[7,8]
- Medication history:
  - A complete list of medications taken is essential. Diuretics, opioids, anticholinergics, and serotonin antagonists are of particular interest.
- Accompanying symptoms:
  - Nausea, vomiting, abdominal pain, cramping.
  - Fever, chills, rigours, and changing cognition may portend a surgical abdomen and may require emergent assessment.

Physical exam

- Abdominal exam:
  - Bowel sounds may be normal or low-pitched and infrequent in constipation. A distended belly and high-pitched sounds may indicate obstruction or ileus. Palpation of the abdomen may reveal a distended bladder, which commonly accompanies severe constipation. Anal inspection may reveal areas of excoriation, erythema, fissures, tears, or fistulae, which may increase discomfort when defecating and may cause patients to resist the urge to pass stool.
- *Rectal exam* is essential to the proper assessment of constipation and should be performed on all consenting patients, except those with severe neutropenia and/or active sepsis. In patients with a history of sexual trauma, however, rectal exam may be deferred. A rectum loaded with stool suggests faecal impaction and severe constipation; while an empty, but ballooned, rectum suggests faecal mass obstructing beyond the reach of the examining finger, an empty and collapsed rectum raises the question of bowel obstruction.[9]
- Volume status exam, including postural vital signs, jugular venous pulsation, and assessing mucous membranes, is important as dehydration may be a cause or consequence of constipation.

In D.C.'s case, the physician did not take a full history or a drug history. He did not examine her and did not perform a rectal exam. No investigations were ordered, and the physician failed to identify the phenomenon of rectal stool impaction with overflow diarrhoea. Instead, her symptoms were dismissed as a viral illness.

Case 8.1 (continued)

D.C. returns home, and her pain and nausea worsen over a period of days and she becomes confused. Returning to the emergency department, she is found to be tachycardic, hypotensive, hypovolaemic, and delirious. Her abdomen is generally tender and has sluggish bowel sounds, but no peritoneal signs. Rectal exam reveals hard stool in the rectum. A plain film of her abdomen shows large amounts of stool throughout her colon. She receives intravenous (IV) fluids, and antiemetics are administered. Several doses of oral PEG 3350,

then bisacodyl and glycerin suppositories are administered, without effect. An enema is considered, but D.C resists and the attending physician instead prescribes an oral bowel purgative containing magnesium oxide, citric acid, and sodium picosulfate. She subsequently passes a large amount of stool.

Question 5. Explain the rationale behind this choice of medication regimen

When constipation prevention fails, causal factors should be identified and treated, whenever possible. In addition, laxatives are invariably needed. Many agents are currently used to treat constipation, as summarized in Table 8.1.

Bulk producers, such as psyllium, add bulk, hydrate and soften stool but are unsuitable for debilitated persons, due to poor fluid intake, and can worsen constipation. Stool softeners are surfactants, increasing faecal water retention but have not shown efficacy in patients receiving palliative care.[6] Lubricants, such as mineral oil, were previously used but are no longer recommended for palliative patients.[4]

Stimulant laxatives produce peristalsis by directly stimulating the myenteric plexus, making them a reasonable choice to combat opioid-induced bowel dysfunction. They may reduce electrolyte absorption and can be associated with cramping. Bedtime dosing or divided dosing (twice a day) is recommended.

Osmotic laxatives, including lactulose, sorbitol, and PEG, are non-absorbable, osmotically active and efficiently draw fluid into the bowel lumen. These agents may be used as first- or second-line agents, particularly for functional constipation or faecal impaction,[10] and may provide long-term benefit.[11] It is wise to increase fluid intake when giving any osmotic laxative. Lactulose and sorbitol have a sweet taste and are associated with bloating and cramps from increased bacterial gas production. PEG is tasteless and does not cause gas production, has better tolerability and superior outcomes compared to lactulose.[12]

Question 6. What rescue therapies are useful for very severe constipation?

Often, severe constipation is treated with suppositories or rectal enemas; however, these treatments may result in patient discomfort and significant embarrassment. In patients with a history of abuse or trauma, rectal therapies should be avoided. Oral saline laxatives can be considered as alternatives. Various saline laxatives may contain ingredients which increase peristalsis, including osmotically active electrolytes such as sodium picosulfate (Pico-Salax®), magnesium citrate (Citro-Mag) or hydroxide, and sodium phosphate. These electrolye-based laxatives are well tolerated and widely used as bowel purgatives prior to colonoscopy.[13] It is also a reasonable option for rescue or refractory constipation before turning to rectal agents. Sodium picosulfate plus magnesium citrate has shown promise in the treatment of chronic constipation.[14] These purgatives differ from osmotic laxatives in that they can be systemically absorbed, raising concerns of electrolyte disturbances, particularly in severe renal dysfunction. Nevertheless, these laxatives can be safely used intermittently as rescue agents as well in most patients.[13]

Rectal laxatives may be necessary when oral laxatives cannot be used or have failed. These treatments can be administered as either enemas or suppositories and generally work in a similar fashion to the orally administered forms. A combination of glycerin (to soften) and bisacodyl (to stimulate) suppositories is often effective for hard stool low in the rectum.

Table 8.1 Agents for treatment of constipation

Type	Onset of action (hours)	Side-effects	Mechanism of action and comments
Bulk agents			
Bran Psyllium Methylcellulose Polycarbophil	12–24	Bloating, flatulence	Increased stool bulk, decreased transit time, increased gastrointestinal motility Require adequate fluid intake *Not recommended in advanced disease*
Stool softeners			
Docusate	12–72	Well tolerated	Detergent activity; softens stool via water retention *Not recommended in advanced disease*
Stimulant laxatives			
Senna Bisacodyl	6–12	Abdominal cramps, electrolyte disturbances	Myenteric plexus stimulation increased motility. decreased absorption of fluid and electrolytes
Osmotic laxatives			
Lactulose Sorbitol Polyethylene glycol	24–48 24–48 0.5–1	Very sweet taste, nausea, abdominal cramps, and flatulence PEG: better tolerated	Non-absorbable molecules draw fluid into intestinal lumen via osmotic forces
Saline laxatives			
Sodium picosulfate Magnesium (citrate, hydroxide, sulfate) Sodium phosphate	1–3	Electrolyte disturbances Avoid in renal insufficiency, heart failure	Osmotically active salts draw fluid into the colonic lumen and stimulate peristalsis May be used as rescue for severe constipation Not to be repeated within 24 hours
Suppositories			
Glycerin Bisacodyl	0.25–1	Rectal irritation	Softening of stool in rectum Induces defecation by distension of rectum Similar to senna
Enemas			
Saline Phosphate Oil retention	5–15 min 5–15 min 6–8	Patient embarrassment Rectal irritation Electrolyte disturbances	Large volume—useful in impaction May be repeated Softens impacted stool

(*continued*)

Table 8.1 Continued

Type	Onset of action (hours)	Side-effects	Mechanism of action and comments
Opioid antagonists			
PAMORAs:			
Methylnaltrexone	1–24	Abdominal pain	No loss of analgesia
Naloxegol			Contraindicated in bowel obstruction
Naloxone	1–3	Opioid withdrawal	Central and peripheral opioid receptor antagonists
Naltrexone		Loss of analgesia	Infrequently used
Other agents			
Lubiprostone		Abdominal pain	Limited availability Increased intestinal fluid secretion via chloride channel activation
Prucalopride		Abdominal pain	$5HT_4$ receptor agonist increases colonic motility

Source: data from Librach S, et al. (2010). 'Consensus Recommendations for the Management of Constipation in Patients with Advanced, Progressive Illness'. J Pain Symptom Manage, 40,761–73 (4); Larkin PJ, et al. (2008). 'The management of constipation in palliative care: clinical practice recommendations'. Palliat Med, 22,796 (5); and Chey WD, et al (2014) 'Naloxegol for Opioid-Induced Constipation in Patients with Noncancer Pain', N Engl J Med, 370(25), 2387–2396. (24)

Commonly used enema preparations are described below:

- Saline laxative enemas. These would include sodium phosphate (Fleet®) and sodium citrate, sodium lauryl sulfoacetate, and sorbitol (Microlax®), among other products. They act both as peristaltic stimulants and as osmotic agents drawing fluid into the stool and can provide rapid bowel clearance. Adverse effects include electrolyte disturbances and rectal irritation and they are best used intermittently. Use with caution in patients with heart failure, renal impairment, seizure disorders, and inflammatory bowel disease.
- Saline. Saline enemas involve administration of large volumes of warmed saline. They may be helpful in patients with impaction of hard, desiccated stool.
- Mineral oil enema. This is most commonly employed as a high enema given overnight to soften and lubricate hard-packed stool. The patient must have the ability to retain the fluid for a prolonged period. This enema also can be administered high in the descending colon with a Foley catheter and the balloon can be inflated for 10–15 minutes to minimize initial returns. A mineral oil retention enema is generally followed by a high saline enema to produce laxation.[4] An oil retention enema can be helpful in patients with a large quantity of stool in the sigmoid colon and rectum who require faecal disimpaction, either before or immediately afterwards, to assist with further removal of stool caught in the sigmoid colon.
- Soap suds enemas can be used as rescue for faecal impaction and have been shown to be more effective than PEG electrolyte solution enemas; however, they were found to be more uncomfortable. There is also a degree of rectal surface epithelium loss after their use.[15]

Case 8.1 (continued)

Further assessment reveals worsening back pain and D.C.'s overall condition has deteriorated. Investigations reveal hypercalcaemia and spinal metastases. She receives IV hydration andpamidronate, as well as a course

of palliative radiation to her thoracic spine, resulting in calcium correction, delirium clearance, and reduced pain. D.C. is discharged home with daily home care services and prescriptions for long-acting morphine 30 mg twice a day, two senna tablets twice a day, and PEG 17 g daily. Her home care nursing team monitors her bowel habits on a daily basis, performs rectal checks PRN. This careful monitoring has resulted in an extended period of stable bowel function.

Question 7. What other investigations would have been helpful in treating this patient's constipation?

As noted previously, the differential diagnosis of constipation is broad, including metabolic, electrolyte, anatomic, and neurologic abnormalities. Investigations for treatable conditions should be considered if within the patient's goals of care:

- *Investigations*:
  - Serum electrolytes, including sodium and potassium levels, anion gap, renal function, and calcium levels, may reveal contributing derangements. Correcting electrolyte disturbances and hypovolaemia may improve gut motility.
- *Imaging*:
  - Flat and upright abdominal X-rays can reveal the extent of the faecal load or can reveal findings suggestive of bowel obstruction or ileus (see Chapter 9). Faecal loading can be quantified by dividing the colon into four segments (ascending, transverse, descending, rectosigmoid), and for each, the amount of stool is scored from 0 to 3, with a maximum score of 12. Any value greater than 7 out of 12 requires intervention.[16]
  - On occasion, computed tomography (CT) of the abdomen with oral contrast may be required to distinguish severe constipation from an obstructed gastrointestinal tract. Imaging of the spine could be considered if there are neurologic findings or known bony metastases.

Case 8.1 (continued)

Two months after discharge, D.C.'s back pain becomes severe again, associated with profound leg weakness. She is again hospitalized, and a spinal cord compression is diagnosed. Her morphine dose escalates and over the next several days, she develops nausea, vomiting, and confusion. Daily bowel movements are documented in her chart. An opioid rotation to hydromorphone is performed due to suspected opioid neurotoxicity. Blood tests are unhelpful in diagnosing any other cause of the confusion. Rectal exam reveals a large amount of very hard-packed stool. X-rays show stool completely filling the bowel lumen, but no air–fluid levels. She is given methylnaltrexone 12 mg subcutaneously, achieving laxation a few hours later. Her cognition returns to normal a few days later, with the delirium a result of opioid neurotoxicity exacerbated by severe constipation.

Question 8. What treatments exist to manage opioid-induced constipation? What is methylnaltrexone?

Opioid receptors exist peripherally, as well as in the central nervous system; opioid action on the bowels is mediated primarily by receptors located in the gastrointestinal tract, resulting in slowed gut motility. OIC can cause significant patient discomfort and its treatment is frequently quite challenging.[17]

If a patient can tolerate oral intake, aggressive doses of combined stimulant and osmotic laxative can achieve laxation, or a mixed saline laxative (Pico-Salex®) could be useful.

Lubiprostone is an oral medication which acts as a chloride channel activator in the small and large intestines, thereby increasing intestinal fluid secretions.[18] It is effective in treating idiopathic constipation and irritable bowel syndrome.[19] Prucalopride is a selective, high-affinity $5HT_4$ receptor agonist which increases colonic motility and transit. Prucalopride increases the frequency of spontaneous bowel movements, compared to placebo, over a 4-week period.[20] Both lubiprostone and prucalopride have been studied in OIC and may provide benefit.[19,20] Very few trials have assessed the efficacy of these agents in palliative care patients, however, and their availability is limited in Canada. For D.C., these agents would not be useful due to her nausea and vomiting. Suppositories or enemas may be poorly tolerated by an agitated patient.

In the past, non-selective opioid antagonists (naloxone, naltrexone) were used to treat OIC. The concern in using these agents is precipitating opioid withdrawal or a pain crisis by affecting central opioid receptors; orally administered naloxone has approximately 3% systemic bioavailability.[21] Peripherally acting mu (μ) opioid receptor antagonists (PAMORAs) are agents that reverse peripheral opioid effects, including constipation, with only limited ability to cross the blood–brain barrier, thereby preserving analgesia. PAMORAs have emerged as an effective therapy for OIC in patients with advanced disease.[17] Methylnaltrexone is an injectable PAMORA, while naloxegol is orally administered. The efficacy of PAMORAs has been shown in patients with advanced illness and OIC, usually providing relief within 4 hours of administration and often within 30 minutes with methylnaltrexone[22,23] and 6 hours with naloxegol.[24] These medications are well tolerated and not associated with systemic opioid withdrawal or reversal of analgesia.[17]

Question 9. How can we improve upon the patient's bowel function, given her current neurological problems?

Bowel management is a common problem in patients with spinal cord compression or cauda equina syndrome. A combination of loss of rectal sensation, loss of voluntary control, poor anal tone, immobility, and pain commonly leads to severe constipation. A cauda equina lesion will abolish the ano-colonic reflex, but a higher spinal cord lesion leaves this reflex intact. In the latter, rectal simulation by suppositories or digitally will stimulate the reflex and colonic contraction will aid evacuation.

The overall goal is achieving 'controlled' or 'scheduled' continence. This often means administering a combination of daily oral laxatives with suppositories (or enemas) every 2–3 days to achieve rectal evacuation, thus avoiding manual disimpaction in these patients with loss of rectal sensation.[25]

Question 10. What are other options for pain control that may optimize D.C.'s bowel function?

Transdermal fentanyl patch is associated with decreased constipation, compared to morphine, in a number of reports.[26,27] Transdermal delivery appears to reduce the effects on opioid receptors in the gut. Methadone has also been reported to reduce constipation and laxative requirements in terminally ill patients.[28] Rotation to methadone often results in a decrease in the total MEDD, which may reduce opioid receptor agonism in the gut.[28] Fixed-dose combinations of naloxone and delayed-release oxycodone (Targin®) have been shown to have analgesic efficacy similar to oxycodone alone, but with improved bowel function, in patients with chronic, non-malignant pain.[29,30]

Case 8.1 (continued)

For the last 4 weeks of her life, D.C. remains in her hospital bed. Her physician orders senna and PEG, along with glycerin and bisacodyl suppositories every 2 days to maintain regularity. Despite her deteriorating condition and poor oral intake, her symptoms remain well controlled. She dies peacefully, with no further bowel concerns.

Summary

It is essential to maintain bowel function through all phases of illness. Constipation contributes to pain, nausea, anorexia, and diminished quality of life. Despite the overwhelming prevalence of constipation and its resultant morbidity, this symptom is often neglected by physicians. However, through careful attention to prevention and maintenance of bowel function, we can significantly improve quality of life for many patients. Factors contributing to constipation must be considered regularly. Finally, severe constipation and opioid-induced constipation require an approach individualized to the patient context and the many treatment choices available.

References

1. **Simren M**, **Palsson OS**, **Whitehead WE** (2017) Update on Rome IV criteria for colorectal disorders: implications for clinical practice. *Curr Gastroenterol Rep*, **19**, 15–22.
2. **Wald A** (2015) Constipation: pathophysiology and management. *Curr Opin Gastroenterol*, **31**, 45–9.
3. **Candy B**, **Jones L**, **Larkin PJ**, **Vickerstaff V**, **Tookman A**, **Stone P** (2015) Laxatives for the management of constipation in people receiving palliative care. *Cochrane Database Syst Rev*, **5**, CD003448.
4. **Librach S**, **Bouvette M**, **De Angelis C** *et al.* (2010) Consensus recommendations for the management of constipation in patients with advanced, progressive illness. *J Pain Symptom Manage*, **40**, 761–73.
5. **Larkin PJ**, **Sykes NP**, **Centano C** *et al.* (2008) The management of constipation in palliative care: clinical practice recommendations. *Palliat Med*, **22**, 796.
6. **Hurdon V**, **Viola R**, **Schroder C** (2000) How useful is docusate in patients at risk for constipation? A systematic review of the evidence in the chronically ill. *J Pain Symptom Manage*, **19**(2), 130–6.
7. **Downing GM**, **Kuziemsky G**, **Lesperance M**, **Lau F**, **Syme A** (2007) Development and reliability testing of the Victoria Bowel Performance Scale (BPS). *J Pain Symptom Manage*, **34**, 513–22.
8. **Hawley P**, **Barwich D**, **Kirk L** (2011) Implementation of the Victoria Bowel Performance Scale (BPS). *J Pain Symptom Manage*, **42**(6), 946–53.
9. **Clark K**, **Currow DC**, **Talley NJ** (2010) The use of digital rectal examinations in palliative care inpatients. *J Palliat Med*, **13**, 797.
10. **Klaschik E**, **Nauck F**, **Ostgathe C** (2003) Constipation—modern laxative therapy. *Support Care Cancer*, **11**, 679–85.
11. **Kamm MA** (2003) Constipation and its management. *BMJ*, **327**, 459–60.
12. **Lee-Robichaud H**, **Thomas K**, **Morgan J**, **Nelson RL** (2010) Lactulose versus polyethylene glycol for chronic constipation (review). *Cochrane Database Syst Rev*, **7**, CD007570.
13. **Jin Z**, **Lu Y**, **Zhou Y**, **Gong B** (2016) Systematic review and meta-analysis: sodium picosulfate/magnesium citrate vs. polyethylene glycol for colonoscopy preparation. *Eur J Clin Pharmacol*, **72**(5), 523–32.
14. **Chan AO** (2012) A pilot study on the efficacy of Picolax given as a four-week course for the treatment of refractory constipation. *Hong Kong Med J*, **18**(5), 388–94.
15. **Schmelzer M**, **Schiller LR**, *et al.* (2004) Safety and effectiveness of large-volume enema solutions. *Appl Nurs Res*, **17**(4), 265–74.

16. **Starreveld JS**, **Pols MA**, **Van Wijk HJ** *et al.* (1990) The plain abdominal radiograph in the assessment of constipation. *Gastroenterology*, **28**, 335–8.
17. **Nee J**, **Zakar M**, **Sugarman MA** *et al.* (2018) Efficacy of treatments for opioid-induced constipation: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*, **16**, 1569–84.
18. **Barish CF**, **Drossman D**, **Johanson F**, **Ueno R** (2010) Efficacy and safety of lubiprostone in patients with chronic constipation. *Dig Dis Sci*, **55**, 1090–7.
19. **Andresen V**, **Layer P** (2002) Medical therapy of constipation: current standards and beyond. *Visc Med*, **34**(2), 123–7. doi: 10.1159/000488695
20. **Sloots C**, **Rykx A**, **Cools M**, **Kerstens R**, **De Pauw M** (2010) Efficacy and safety of prucalopride in patients with chronic noncancer pain suffering from opioid-induced constipation. *Dig Dis Sci*, **55**, 2912–21.
21. **Liu M**, **Wittbrodt E** (2002) Low-dose oral naloxone reverses opioid-induced constipation and analgesia. *J Pain Symptom Manage*, **23**, 48–53.
22. **Thomas J**, **Karver S**, **Cooney GA** *et al.* (2018) Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med*, **358**, 2332–43.
23. **Slatkin N**, **Thomas J**, **Lipman AG** *et al.* (2009). Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. *J Support Oncol*, **7**, 39–46.
24. **Chey WD**, **Webster L**, **Sostek M** *et al.* (2014) Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med*, **370**(25), 2387–96.
25. **Fallon M**, **O'Neill B** (1997) ABC of palliative care: constipation and diarrhoea. *BMJ*, **315**, 1293–6.
26. **Ahmedzai S**, **Brooks D** (1997) Transdermal fentanyl versus sustained release oral morphine in cancer pain: preference, efficacy, and quality of life. *J Pain Symptom Manage*, **13**, 254–61.
27. **Allan L**, **Hays H**, **Jensen N-H** *et al.* (2001) Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *BMJ*, **322**, 1–7.
28. **Daeninck PJ**, **Bruera E** (1999) Reduction in constipation and laxative requirements following opioid rotation to methadone: a report of four cases. *J Pain Symptom Manage*, **18**, 303–9.
29. **Löwenstein O**, **Leyendecker P**, **Eberhard AL** *et al.* (2010). Efficacy and safety of combined prolonged release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. *BMC Clin Pharmacol*, **10**, 12.
30. **Simpson K**, **Leyendecker P**, **Hopp M** *et al.* (2008) Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate-to-severe noncancer pain. *Curr Med Res Opin*, **24**, 3503–12.

Chapter 9

Malignant bowel obstruction

Carl Bromwich

Attitude

To enable each learner to:

- Recognize the impact of malignant bowel obstruction (MBO) on the quality of life and prognosis of affected patients.
- Identify the roles of different disciplines in the management of MBO.

Skills

To enable each learner to:

- Make a diagnosis of MBO using a focused history and physical exam, as well as, where appropriate, other diagnostic procedures.
- Distinguish between the different mechanisms of bowel obstruction in the cancer patient.
- Integrate patient preferences and objectives of care in the formulation of a treatment plan for MBO.

Knowledge

To enable each learner to:

- Prescribe pharmacological interventions appropriate to the different circumstances and symptoms associated with MBO and to understand the evidence or the lack thereof supporting said interventions.
- Recognize the place of surgical intervention in the management of MBO.
- Recognize the place of self-expanding metallic stents (SEMS) in the management of MBO.
- Recognize the contribution of the nutritionist in the management of MBO.

Case 9.1

C.C. is a previously healthy 68-year-old man who presented to his family doctor with a history of several months of intermittent left-sided abdominal discomfort. He reported worsening and more frequent crampy pain associated with bloating, nausea, and a striking narrowing of his stool calibre. Blood tests revealed iron deficiency anemia. He was referred for an urgent consultation with the gastroenterologist. By the time he was seen, he was passing minimal stool, had frequent episodes of vomiting and nearly continuous 6/10 abdominal pain, and had lost 7 kg. A colonoscopy revealed a stenosing adenocarcinoma of the descending colon; subsequent exams revealed a solitary right-sided hepatic metastasis, with no evidence of peritoneal carcinomatosis. His Palliative Performance Scale v2 (PPSv2) was estimated to be 80%.

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Question 1. What is malignant bowel obstruction and how common is it?

Simple versus malignant bowel obstruction

A simple bowel obstruction may be defined as any process restricting the normal flow of bowel contents and includes many causes that do not meet the criteria for MBO as determined in a 2007 consensus statement. According to this consensus, MBO is defined by the following criteria:

1. Clinical evidence of a bowel obstruction (via history/physical/radiographic examination).
2. Bowel obstruction beyond the ligament of Treitz.
3. Intra-abdominal primary cancer with incurable disease.
4. Non-intra-abdominal cancer with clear intraperitoneal disease.[1]

Primary abdominal and pelvic malignancies are frequently complicated by MBO, including up to 51% of women with recurrent ovarian cancer and 25–40% of patients with metastatic colorectal cancer.[2,3]

Benign versus malignant bowel obstruction

The aetiology of bowel obstruction in the cancer patient may be benign (most commonly post-surgical adhesion in the small bowel or severe constipation in the large bowel) or malignant from tumour-related factors.

Functional versus mechanical bowel obstruction

It is important to determine if MBO is functional or mechanical. Non-obstructive processes, such as paralytic ileus (also known as pseudo-obstruction or functional bowel obstruction), may result in clinical situations that resemble MBO and may coexist with MBO. Paralytic ileus is often seen following surgical intervention, especially if the bowel has been manipulated. Other causes include peritonitis, bowel ischaemia, hypokalaemia, retroperitoneal haemorrhage, and mediation effects. Paralytic ileus is distinguished from mechanical obstruction by minimal or absent bowel sounds and by the uniform distribution of gas throughout the bowel on abdominal radiographs. Mechanical aetiologies include intraluminal obstruction (more common in the large bowel) and extra-luminal compression (more common in the small bowel). Table 9.1 lists the causes of bowel obstruction in patients with cancer.[4,5]

Proximal versus distal and partial versus complete bowel obstruction

The clinical presentation of MBO is, in part, related to the level of the obstruction (proximal versus distal) and it is important to classify the nature of the obstruction (partial versus complete), as it has implications for the approach to management. More proximal obstructions are liable to be associated with more vomiting and less abdominal distension, while more distal obstructions often have an insidious onset of symptoms, with constipation as an associated feature. Nausea and colicky abdominal pain are common symptoms, irrespective of the site of the obstruction. A partial bowel obstruction typically allows for the passage of some stool and flatus, while a complete bowel obstruction is characterized by the inability to pass stool and flatus, resulting in a more dramatic presentation and more disastrous consequences in the absence of relief from the obstruction. A partial MBO will often progress to a complete obstruction over time.

Table 9.1 Differential diagnoses of bowel obstruction in cancer patients

Aetiology	Pathophysiology
Constipation	Faecal impaction
Adhesion	Malignant Post-operative Post-radiation Post-infectious
Malignant mass	Single or multiple (e.g. peritoneal carcinomatosis) Intraluminal mass Extra-luminal compression Intussusception
Strangulatoin	Around tumour Around adhesions
Ileus	
Ascites	Drugs Peritonitis, haemoperitoneum
Non-malignant mass	Abscess Phlegmon Anastomotic or ischaemic stricture Medical device migration

Source: data from Mercadante, S. 'Palliative care of bowel obstruction in cancer patients.' UpToDate. Waltham, MA: UpToDate Inc, Wolters Kluwer, https://www.uptodate.com; and Franke et al. 'Management of malignant bowel obstruction associated with GI cancers'. J Oncol Rev, Vol. 13, Issue 7, pp.426–434, 2017 American Society of Clinical Oncology.

A clinical suspicion of MBO should be confirmed objectively by diagnostic imaging. A plain film of the abdomen is the simplest, most cost-effective means of confirming the diagnosis of MBO. Figures 9.1 shows the classic features of a small bowel obstruction, namely dilated bowel loops and air–fluid levels. A CT scan of the abdomen can also be useful and often yields more detailed information regarding the site and, frequently, the nature of the obstruction.

While C.C.'s initial presentation is technically a distal MBO, the management of curative disease is not the focus of this chapter.

Case 9.1 (continued)

C.C. was found to be dehydrated and was admitted to hospital where pain relief was achieved with regular doses of a short-acting opioid. Nausea was relieved with haloperidol and a self-expanding stent was successfully inserted to decompress the colon and allow for planning of an elective left hemicolectomy with primary re-anastomosis, which was accomplished 7 days following the stent placement. One month later, he had a hepatic metastasectomy, followed by adjuvant chemotherapy. He was well thereafter, returning to his normal activities without difficulty (PPSv2 = 90%).

One year after finishing his adjuvant chemotherapy, he presented to the emergency room with a history of acute onset of nausea and vomiting 2 days before. He was unable to eat or drink. He had passed neither flatus nor stool in that time. He reported that he had been having abdominal discomfort, nausea, and occasional vomiting, especially after eating for several weeks prior to the current episode. A plain film of the abdomen revealed gastric and proximal small bowel dilatation (PPSv2 = 80%).

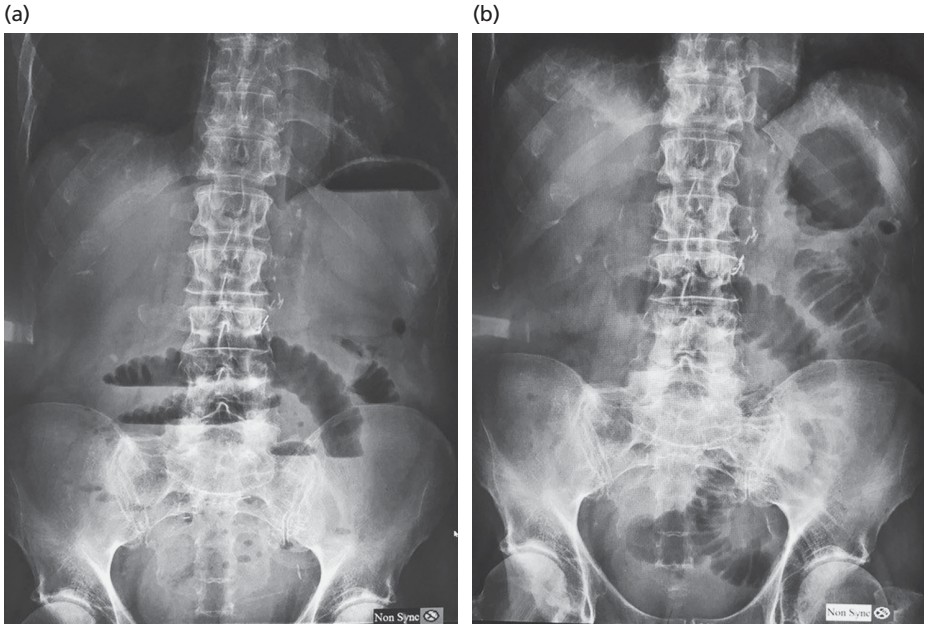


Fig. 9.1 Plain films of the abdomen revealing an obstructed small bowel with dilated loops and air–fluid levels.
Reproduced courtesy of Dr. Lucie Brazeau, Université de Sherbrooke, Québec, Canada.

Question 2. What factors influence the use of invasive interventions for MBO?

MBO is classically associated with advanced disease. In addition to the most important factor, which is the patient's goals of care, the functional status of the patient helps to determine whether invasive procedures, such as surgery and stenting, should be considered. If a person is not a surgical candidate or in the absence of a surgical emergency, the initial approach to management includes a trial of pharmacological treatment for symptom reduction, with or without enteric tube decompression for relief of vomiting. In advanced illness, medical management and decompression may be the only reasonable therapeutic intervention.

Question 3. What is the role of surgery in the management of malignant bowel obstruction?

Potential surgical interventions include resection of the obstruction with or without re-anastomosis, an intestinal stoma, a bypass of the obstructed segment, and a venting gastrostomy for symptom relief. Morbidity (42%) and operative mortality are high (5–32%) and re-obstruction is common (10–50%).[4] Surgical options are generally considered for the subset of patients for whom restoration of intestinal function would provide the opportunity to pursue further treatment of the underlying malignancy. Surgery is not indicated for those who are imminently dying.[2,3,6]

Certain parameters are associated with a low likelihood of benefit from surgical intervention. These include:[2,3,5,6]

- Complete small bowel obstruction.
- Non-gynaecological cancer.

- Ascites.
- Depressed serum albumin.
- Abnormal total white blood cell count.
- Age >65.
- Extensive peritoneal carcinomatosis.
- Multi-level obstruction.
- Poor functional status.

On the other hand, radiographic evidence of a single transition point may increase the probability of an acceptable surgical outcome.[5]

Unfortunately, there exists no high-quality evidence to define the role of surgery in the management of symptoms associated with MBO, as evidenced by a recent Cochrane systematic review.[7]

Question 4. What role do self-expanding stents play in the management of malignant bowel obstruction?

SEMS have been used in the management of malignant large bowel obstruction since the 1990s. Acute malignant colorectal obstruction is a common condition (up to 29% of patients with colorectal carcinoma) attended by high morbidity and mortality and must be relieved urgently when the patient's goals of care are consistent with an invasive intervention. In patients with acceptable surgical risk [age <70, American Society of Anesthesiologists (ASA) score <III], primary surgical management is the preferred option; however, in high-risk patients SEMS are employed as a 'bridge to surgery' or for non-operable situations where there is a single site of obstruction that is amenable to stenting.[3,8,9] Stenting can be used to relieve symptoms of obstruction in non-surgical candidates, even in the setting of advanced disease. The American and European Societies of Gastrointestinal Endoscopy state that 'SEMS placement is the preferred treatment for palliation of malignant colonic obstruction', except in patients treated with anti-angiogenic chemotherapy (bevacizumab).[9]

Traditionally, stenting of obstructive intestinal lesions is limited to the large bowel and the proximal duodenum, by virtue of the inaccessibility of the rest of the small bowel to endoscopy. There are some reports in the literature regarding both endoscopic and transcutaneous placement of jejunal stents which demonstrate some successes in palliation; however, more evidence is required before these techniques have broad support.[10,11] Both stenting and surgery appear to provide some survival benefit (months), compared with non-invasive supportive care, in a small subset of patients without contraindications.

Case 9.1 (continued)

A CT scan of the abdomen revealed a transition point in the proximal jejunum felt to be consistent with an obstruction due to an adhesion; there was no evidence of recurrent cancer and his carcinoembryonic antigen (CEA) remained in the normal range. Conservative treatment of the obstruction was unsuccessful; however, laparoscopic lysis of the adhesion resulted in complete resolution of all symptoms (PPSv2 = 90%).

After 3 more years of living without significant symptoms, C.C.'s usual cancer surveillance revealed a spike in his CEA. Subsequent investigations revealed multiple hepatic metastases and several small peritoneal implants. He remained asymptomatic and opted for palliative chemotherapy. He tolerated the therapy well and remained minimally symptomatic, without significant progression of disease, for another year. Thereafter, he began to suffer from intermittent bouts of colicky abdominal pain, associated with nausea and bloating. After 2 days of nearly continuous discomfort, he presented to the emergency room where a plain film of the

abdomen revealed multiple air–fluid levels without significant bowel distension. A CT scan of the abdomen revealed progressive peritoneal carcinomatosis, with a moderate amount of ascites and multiple levels of partial small bowel obstruction (PPSv2 = 70%).

Question 5. What pharmacological options are available in the management of MBO?

C.C. is now suffering from symptoms of a partial small bowel obstruction resulting from peritoneal carcinomatosis. The clinical picture is the result of a cycle of accumulation of gastrointestinal secretions with third spacing of fluids, intestinal distension, smooth muscle spasm, and mucosal oedema. He is not a candidate for surgical intervention or stenting, and supportive management is the focus of treatment and he is admitted for symptom management. In the context of MBO from peritoneal carcinomatosis with no further disease-modifying therapies, prognosis is measured in weeks to months, so it is important to address C.C.'s understanding of his illness and to review goals of care.

If consistent with the patient's goals of care, intravenous hydration is appropriate during the initiation of symptom management as spontaneous resolution of the obstruction will occur in up to 30% of patients.[5] In the short term, significant symptom relief can be achieved with decompression by nasogastric intubation; however, the goal should be pharmacologic symptom control, allowing for the removal of the tube and the avoidance of the complications associated with prolonged placement (nasopharyngeal discomfort, nasal cartilage erosion, bleeding, otitis, aspiration pneumonia, oesophagitis). As he was not vomiting, C.C. did not require a nasogastric tube for symptom relief; however, he received nothing by mouth.

Analgesia is an essential aspect of symptom control and should be achieved acutely with regular dosing of parenteral opioids, typically morphine or hydromorphone, as well as PRN dosing for breakthrough pain. While opioids are frequently efficacious for colicky pain, an anticholinergic agent such as hyoscine butylbromide may be used as an adjuvant in the management of colic. C.C. is prescribed morphine 5 mg subcutaneously (SC) q4h and 2.5 mg SC q1h PRN, which results in rapid improvement in his pain. Once pain control has been achieved, a rotation to transdermal fentanyl should be considered if the patient is well enough to return home and ongoing analgesia is necessary. Recurrent obstruction is very common in this context and the transdermal route will likely provide more reliable baseline analgesia than oral agents.

Nausea and vomiting may be incapacitating in patients with MBO and the goal of treatment should be to reduce the intensity/frequency of these symptoms to a level that is acceptable to the patient. Many different agents may help to achieve this goal, including phenothiazines, butyrophenones, 5-hydroxytryptamine receptor agonists, dopamine antagonists, anticholinergics, anti-secretory agents (e.g. ranitidine), and somatostatin analogues. A 2010 review suggested that there is moderate evidence to support the use of metoclopramide in the context of partial obstruction without the presence of colic.[12,13] C.C. has colic, however, and the use of a prokinetic agent is liable to exacerbate, rather than alleviate, his symptoms. A centrally acting dopamine antagonist, such as haloperidol, would be an excellent choice of antiemetic in this situation. Again, whatever the choice, a parenteral route is preferred in patients whose gastrointestinal function is compromised. C.C. receives haloperidol 1 mg SC q8h.

The role of corticosteroids in the management of MBO was evaluated in a Cochrane review and the result was indeterminate, though there was a suggestion that they may help in relieving obstruction and that the rate of adverse events attributable to corticosteroids was very low.[14] In

any case, the anti-inflammatory, antiemetic, and analgesic properties of corticosteroids make them a mainstay in the treatment of MBO and C.C. receives dexamethasone 4 mg SC twice a day (morning and noon). Corticosteroids are ideally given early in the day to avoid potential insomnia.

Case 9.1 (continued)

C.C. responded quickly to his new medications and was soon able to tolerate liquids without recurrent colic. Ultimately, he returned home with a transdermal fentanyl patch 12 mcg/hour, a tapering dose of dexamethasone, and haloperidol PRN for nausea (PPSv2 = 50%).

In consultation with his oncologist, C.C. decided to discontinue palliative chemotherapy in the interest of focusing instead on symptom management and quality of life. Over the next 6 weeks, he was admitted to the hospital twice more for recurrent episodes of more severe abdominal pain associated with bloating, nausea, and vomiting. At the time of the second admission, he was found to have a complete obstruction of the small bowel and his vomiting was intolerable. A nasogastric tube was inserted at the time of admission (PPSv2 = 40%).

When standard treatment with corticosteroids, antiemetics, and analgesics is insufficient, anti-secretory drugs are frequently considered as a means of reducing gastrointestinal secretions and thereby reducing vomiting, distension, and pain.

There is evidence to support the use of proton pump inhibitors or histamine 2 antagonists to reduce gastric secretions in MBO, though the best option appears to be ranitidine.[13,15]

Somatostatin analogues (usually octreotide) are often used in preference to anticholinergic, anti-secretory drugs, such as hyoscine butylbromide, which are less expensive. While some individual studies have shown somatostatin analogues to be superior to other anti-secretory agents, a recent randomized controlled trial, as well as a systematic review of the literature evaluating this agent, found no good evidence to support using the more expensive agent to reduce vomiting, compared to management with dexamethasone and ranitidine alone.[16,17] At the time of his most recent admission, however, C.C. was already using a fentanyl patch, haloperidol, hyoscine butylbromide, ranitidine, and dexamethasone. In the hope of relieving him of his nasogastric tube and allowing him to return home once more, octreotide was started. The usual starting dose is 100 mcg SC q8h. Daily titration to effect is reasonable up to a dose of 300 mcg SC q8h. If effective, a long-acting intramuscular form of the drug is available, simplifying care at home as the dosing frequency is every 28 days. The short-acting form should be continued for 6 days, following the initial injection of the long-acting form.[13]

Case 9.1 (continued)

C.C. improved. His nasogastric tube was successfully removed, and he returned home where he was able to tolerate small amounts of liquid, as well as occasional liquid nutritional supplements. Unfortunately, after 3 weeks of reasonable comfort, he began vomiting again (PPSv2 = 30%).

Question 6. What interventions may be considered when pharmacological management fails?

When symptom control is unacceptable in spite of what might well be considered maximum pharmacotherapy, then decompression and symptom relief may be achieved with a venting

gastrostomy if this level of intervention is consistent with the patient's goals of care. Percutaneous endoscopic gastrostomy tube placement by interventional radiology techniques are much more common than an open surgical approach. Symptom control is usually achieved, no matter the technique.[18] Large-volume ascites was once considered a contraindication; however, recent data demonstrate that it is technically feasible.[19] The procedure is not without risk. One series reported major adverse events in nearly 10% of patients, including peri-gastrostomy leakage of ascites, peritonitis and, in one case, death.

Case 9.1 (continued)

C.C.'s remaining goals were to see his son who was living overseas, to hold his first grandchild, and not to see the inside of another hospital. He agreed to a venting gastrostomy for symptom control. He was able to stay at home for another 4 weeks, managing intermittent exacerbations of symptoms with the use of his gastrostomy. In between episodes, he managed some intake of nutritional supplements, however, his ability to take anything by mouth was increasingly compromised (PPSv2 = 20%).

Question 7. Does parenteral nutrition have any role in the management of MBO?

While parenteral nutrition is sometimes used to support patients with MBO who are receiving palliative chemotherapy as a potential means of reversing MBO, there is little evidence to support the use of palliative chemotherapy to this end.[2,5,20] It can also be used as a bridge for nutrition when interventions to reverse MBO, such as surgery, are being planned. In general, total parenteral nutrition (TPN) has not been shown to improve survival or quality of life in the setting of irreversible MBO from end-stage disease. A recent Cochrane systematic review assessed the effectiveness of home parenteral nutrition with regard to improvements to survival and to quality of life. The evidence was insufficient to answer either question.[21] Few would support the broad use of parenteral nutrition in patients with MBO, however, in rare circumstances it may be the tool that allows the patient to attain their goals of care.[22,23] As with any treatment under consideration, discussion of the potential risks and benefits, however ill-defined, is warranted prior to initiating therapy.

Case 9.1 (continued)

Shortly after meeting his grand-daughter, C.C.'s venting gastrostomy ceased to provide any relief from constant nausea and frequent vomiting, which had become unresponsive to pharmacological interventions. His PPSv2 was 20% and it was apparent that he was in the last days of life, so his request for palliative sedation to definitively relieve his symptoms was honoured. He died at home 4 days later, very comfortable and surrounded by his family.

Conclusion

MBO is a common occurrence in patients with advanced cancer. The treatments offered should reflect the patient's goals of care and their performance status. Interventions for potentially curable or reversible aetiologies should be considered, and treatments range from conservative medical management to more invasive interventions, when appropriate, including surgery, stents, and

venting nasogastric or percutaneous gastrostomy tubes. The primary goal is to relieve distress and optimize symptom control, whenever possible.

References

1. **Thomas A**, **Baron T**, **Mercadente S** *et al.* (2007) Report of the clinical protocol committee: development of randomized trials for malignant bowl obstruction. *J Pain Symptom Manage*, **34**(suppl 1), S49–59.
2. **Lee YC**, **Jivraj N**, **O'Brien C** *et al.* (2018) Malignant bowel obstruction in advanced gynaecological cancers: an updated review from a multidisciplinary perspective. *Obstet Gynecol Int*, 2018, 1867238.
3. **Roses RE**, **Folkert I**, **Krouse RS** (2018) Malignant bowel obstruction: Reappraising the value of surgery. *Surg Oncol Clin North Am*, **27**, 705–15.
4. **Mercadante S** (2020) *Palliative care of bowel obstruction in cancer patients*. https://www.uptodate.com
5. **Franke AJ**, **Iqbal A**, **Starr JS** *et al.* (2017) Management of malignant bowel obstruction associated with GI cancers. *J Oncol Rev*, **13**(7), 426–34.
6. **Ferguson HJM**, **Ferguson CI**, **Speakman J** *et al.* (2015) Mangement of intestinal obstruction in advanced malignancy. *Ann Med Surg*, **4**, 264–70.
7. **Cousins SE**, **Tempest E**, **Feuer D** (2016) Surgery for the resolution of symptoms in malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database Syst Rev*, **1**, CD002764.
8. **Shimura T**, **Takashi J** (2016) Evidence-based clinical management of acute malignant colorectal obstruction. *J Clin Gastroenterol*, **50**, 273–85.
9. **van Hooft JE**, **van Halsema EE**, **Vandbiervliet G** *et al.* (2014) Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy*, **46**, 990–1002.
10. **Tsuboi A**, **Kuwai T**, **Nishimura T** *et al.* (2016) Safety and efficacy of self-expandable metallic stents in malignant small bowel obstructions. *World J Gastroenterol*, **22**(40), 9022–7.
11. **Kim J**, **Yoon CJ**, **Seong NJ** (2018) Transjejunostomy stent placement in patients with malignant small-bowel obstructions. *AJR Am J Roentgenol*, **211**(5),1148–54.
12. **O'Connor B**, **Creedon B** (2011) Pharmacological treatment of bowel obstruction in cancer patients. *Expert Opin Pharmacother*, **12**(14), 2205–14.
13. **Laval G**, **Marcelin-Benazech B**, **Guirimand F** *et al.* (2014) Recommendations for bowel obstruction with peritoneal carcinomatosis. *J Pain Symptom Manage*, **48**(1), 75–91.
14. **Feuer DDJ**, **Bradley KE** (2000) Corticosteroids for the resolution of malignant bowel obstruction in advanced gynecological and gastrointestinal cancer. *Cochrane Database Syst Rev*, **1**, CD001219.
15. **Clark K**, **Lam L**, **Currow D** (2009) Reducing gastric secretions—a role for histamine 2 antagonists or proton pump inhibitors in malignant bowel obstruction? *Support Care Cancer*, **17**(12), 1463–8.
16. **Currow DC**, **Quinn S**, **Agar M** *et al.* (2015) Double-blind, placebo-controlled, randomized trial of octreotide in malignant bowel obstruction. *J Pain Symptom Manage*, **49**(5), 814–21.
17. **Obita GP**, **Boland EG**, **Currow DC** *et al.* (2016) Somatostatin analogues compared with placebo and other pharmacologic agents in the management of symptoms of inoperable malignant bowel obstruction: a systematic review. *J Pain Symptom Manage*, **52**(6), 901–19.
18. **DeEulis TG**, **Yennurajalingam S** (2015) Venting gastrostomy at home for symptomatic management of bowel obstruction in advanced/recurrent ovarian malignancy: a case series. *J Palliat Med*, **18**(8), 722–8.
19. **Shaw C**, **Bassett RL**, **Fox PS** *et al.* (2013) Palliative venting gastrostomy in patients with malignant bowel obstruction and ascites. *Ann Surg Oncol*, **22**(2), 497–505.
20. **Dean E**, **Khoja A**, **Clamp L** *et al.* (2017) Malignant bowel obstruction in advanced ovarian cancer. *Future Oncol*, **13**(6), 513–21.
21. **Sowerbutts AM**, **Lal S**, **Sremanakova J** *et al.* (2018) Home parenteral nutrition for people with inoperable malignant bowel obstruction. *Cochrane Database Syst Rev*, **8**, CD012812.

22. **Bozetti F**, **Arends J**, **Lundholm A** et al. (2009) ESPEN guidelines on parenteral nutrition: non-surgical oncology. *Clin Nutr*, **28**(4), 445–54.
23. **Naghibi N**, **Smith TR**, **Elia M** (2015) A systematic review with meta-analysis of survival, quality of life and cost-effectiveness of home parenteral nutrition in patients with inoperable malignant bowel obstruction. *Clin Nutr*, **34**(5), 824–37.

Chapter 10

Anorexia–cachexia

Vickie Baracos and Neil MacDonald

Attitude

To enable each learner to:

- Realize the common aetiology driving the progress of cancer and other chronic diseases and anorexia–cachexia.
- Reflect on the serious import of anorexia–cachexia on patient and family suffering.
- Consider the high priority that must be assigned to anorexia–cachexia; recognition, assessment, management, and research in all chronic disorders.
- Realize the essential role of allied health professionals as team members addressing nutritional issues.
- Realize the critical role of both patients and families as members of the team combating nutritional problems.
- Realize that symptom management and specific disease therapies must be given equal status and fully integrated throughout the course of illness.

Skills

To enable each learner to:

- Diagnose anorexia–cachexia as early as possible in a patient's course.
- Demonstrate proficiency in establishing a plan for assessment of nutritional problems in patients.
- Demonstrate competence in identifying new research leads and integrating them into practice.

Knowledge

To enable each learner to:

- Describe the pathophysiology of anorexia–cachexia and establish clinical practices based on the pathophysiology.
- Develop a checklist to identify problems which contribute to anorexia–cachexia which can be ameliorated by specific therapies.
- Describe the chronic inflammatory process as it applies to disease progression and symptomatology.
- Cite the components of a nutritional plan for patients and families.
- Recognize the appropriate use of current dietary supplements and drug therapies.

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Introduction

Anorexia–cachexia afflicts a high proportion of patients with cancer and other chronic diseases in their advanced stages. Anorexia–cachexia is a problem which may be most clearly appreciated by caregivers, whose effort to adopt a nourishing role is frustrated. An onerous burden of care inexorably falls upon them, affecting their own health, mobility, and savings. For many patients, anorexia–cachexia commonly results in hospitalization for prolonged periods, thus further creating costs for their families and the State where public health programmes exist.

Notwithstanding its importance, the anorexia–cachexia syndrome has not been a research priority. Consequently, until recently, little was known about its aetiology and little could be done to prevent or correct its devastating outcomes.

This grim scenario is now changing. It is important to identify the anorexia–cachexia syndrome early in the trajectory of illness and to address it vigorously; turning attention to it only late in the illness will result in futile efforts.

Case 10.1

C.L., a 53-year-old teacher with a husband and two young adult children, presented to the emergency department with an episode of severe epigastric pain. She had 'not felt well' for about 8 weeks, noting onset of a poor appetite, low-grade abdominal discomfort, early satiety, and fatigue. Her body mass index (BMI) is 24 kg/m^2 and over the recent 3 months, she has lost 12% of her body weight. Critical laboratory findings included abnormal liver function tests and markers of a chronic inflammatory state—elevated C-reactive protein (CRP) of 32 mg/l and neutrophil/lymphocyte ratio of 5.2. A diagnosis of adenocarcinoma of the pancreas was made, with widespread liver metastases, accompanied by anorexia–cachexia.

Despite her symptom burden, C.L. is fully active (performance status 90%) and committed to maintaining her family and professional responsibilities.

Question 1. What are the definitions of anorexia and cachexia?

Weight loss is the sentinel indicator of anorexia–cachexia. Weight loss is typically graded according to its severity (see Figure 10.1), from absent (Grade 0) to Grade 4 which is defined by high weight loss and low BMI. Weight loss grades were established based on their association with mortality.[1]

An expert international panel published a definition of cancer-associated cachexia in 2011:[2]

> *… a multi-factorial syndrome [of involuntary weight loss] defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support. It leads to progressive functional impairment. Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.*[1]

[1] Reproduced with permission from Fearon K, et al. 'Definition and classification of cancer cachexia: an international consensus'. Lancet Oncol. Vol 12, Issue 5, pp. 489–95. Copyright © 2011 Elsevier Ltd.

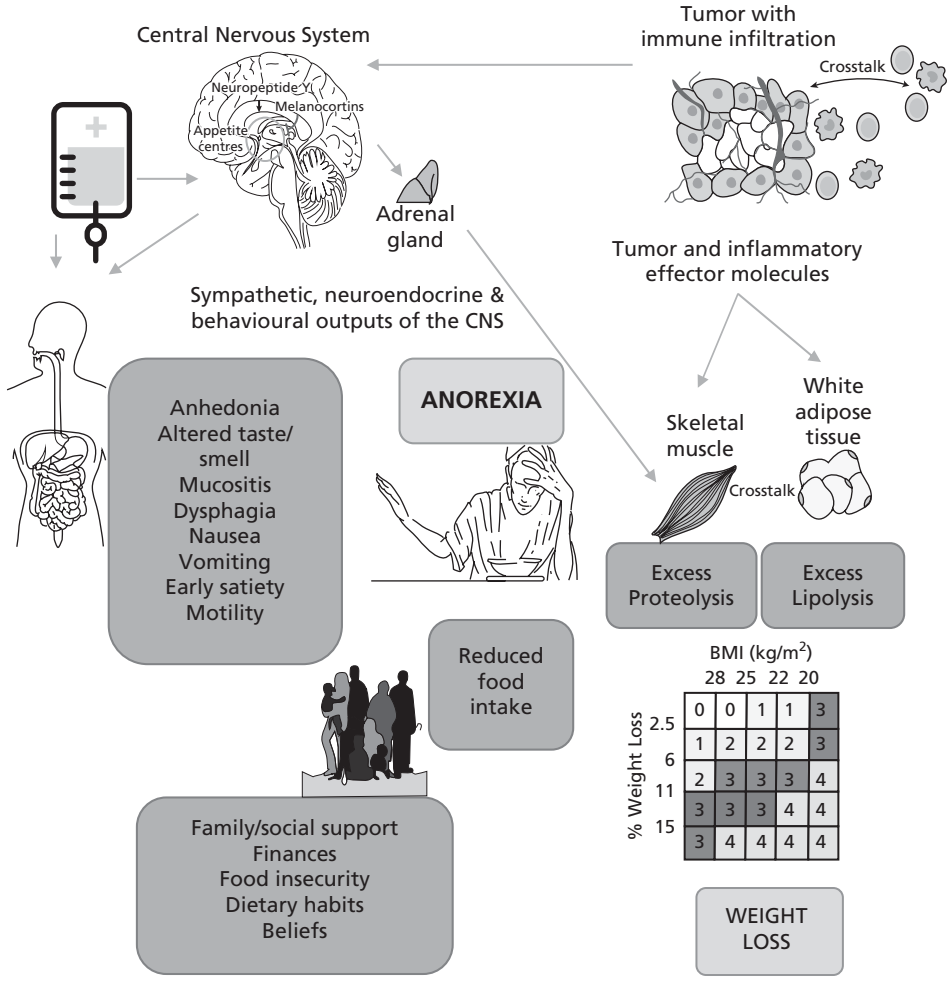


Fig. 10.1 A model of anorexia–cachexia aetiology.

Question 2. What are the clinical characteristics of patients with the anorexia–cachexia syndrome?

As illustrated by C.L., patients exhibit a host of seemingly disparate manifestations. These are presented in Box 10.1.

Question 3. What is the pathophysiology of anorexia–cachexia?

Cancer cachexia is driven by a variable combination of reduced food intake and altered metabolism.[2] Of note, tumours and host cells produce a complex mixture of molecules that are actors in anorexia–cachexia (see Figure 10.1). Also, tumour interactions with the immune system[3] elicit a panoply of pro-inflammatory molecules, including eicosanoids and cytokines [interleukin (IL)-1 and -6, interferon γ, tumour necrosis factor (TNF) α, and transforming growth factor (TGF)-β

Box 10.1 Anorexia–cachexia: manifestations and metabolic changes*

Symptoms

- Weight loss
- Anorexia
- Fatigue
- Depression
- Early satiety
- Reduced function

Biologic features

- Markers of chronic inflammation, notably raised CRP, elevated neutrophil:lymphocyte ratio; immune cell activation and secretion of factors which enhance both tumour growth and anorexia–cachexia
- Increased resting energy expenditure and increased autonomic sympathetic activity
- Low albumin (late finding)
- Low testosterone (men)
- Tumour and immune cell production of catabolic effector molecules

* All or several of the below may be present.

and its cousins (e.g. activin A, myostatin, growth and differentiation factor (GDF)-15], as well as an assortment of other molecules.

The specific aetiology of anorexia–cachexia in individual patients requires further elucidation. Altered metabolism remains the most challenging aspect. For most of the catabolic effector molecules, there is not currently a means of modifying their production or action, but these are considered potential therapeutic targets for anti-cachexia therapy.

A variety of molecules derived from the tumour, or resulting from tumour interactions with the host immune system, can mediate effects on the central nervous system (CNS), evoking a decreased central drive to eat. Cancer-related pain or nausea also suppresses the central drive to eat. Some of the reduced food intake is secondary to cancer treatments. Common side-effects of cytotoxic chemotherapy include anorexia, nausea, and vomiting, which are nutritionally impactful symptoms and these effects can be substantial. Psychosocial factors can also act as barriers to food intake, for example, mood disorders, food insecurity, lack of social support for assistance with meal preparation, and poor dietary habits.

Anorexia

Nutrients are not ingested in sufficient quantity to maintain positive energy and protein balance in patients with cancer.[2] Lack of appetite is pervasive, with many patients reporting no feelings of hunger at any time.

The CNS exerts overarching control of food intake (see Figure 10.1). Sickness behaviours (which include anorexia and catabolism of lean body tissues), fever, and lethargy comprise a programme of responses common to acute and chronic illness, including cancer. Available evidence supports a model wherein cytokine signals are amplified within the CNS, generating inflammation that, in turn, initiates and sustains alterations in the activity of neuronal populations that regulate appetite, metabolism, and body weight.[3]

Understanding of CNS circuits involved in cancer anorexia is improving.[3,4] Cancer anorexia has been associated with calcitonin gene-related peptide neurons in the parabrachial nucleus that transmit anorexic signals. GDF-15 is also implicated in cancer anorexia and its receptor was recently identified as a new CNS circuit in body weight regulation and is expressed in the area postrema. Agouti-related protein (AgRP), the endogenous antagonist at the hypothalamic melanocortin-4 receptor (MC-4R), reverses anorexia and increases metabolism in cancer cachexia.

Muscle loss

Inflammatory activity brings about the activation of atrophy genes which activate endogenous proteolytic systems (ubiquitin–proteasome system, autophagy), disturbing the balance between muscle synthesis and catabolism. Probably both circulating cytokines and cytokines upregulated within the muscle are involved in this process.[3] Inflammatory cytokines additionally inhibit the anabolic effects of growth hormone and insulin-like growth factor and induce insulin resistance, thus contributing to reduced muscle synthesis. Members of the TGF-β family, myostatin, activin A, and GDF-11 are commonly upregulated in cachexia and further contribute to excess catabolism.

Muscle wasting is also chemotherapy-related;[5] cytotoxic agents (e.g. oxaliplatin, cisplatin, anthracyclines, 5-fluorouracil, irinotecan) are taken up by muscle cells and induce atrophy, mitochondrial dysfunction, oxidative damage, cellular energy depletion, and apoptotic or necrotic cell death.

Fat loss

The precise physiological controls on *de novo* lipogenesis and lipolytic pathways that allow for an overall state of neutral fat balance in healthy individuals are modified in cancer cachexia. Response to normal physiological regulators is aberrant—there is loss of the inhibitory action of insulin with concurrent hypersensitivity of lipolysis by catecholamines and natriuretic peptides, resulting in overexpression and activation of hormone-sensitive lipase. Tumours secrete potent lipolysis-inducing factors, including IL-6, TNF-α, zinc-α2-glycoprotein, adrenomedullin, and parathyroid hormone-related protein.[3,5]

Pain and symptoms

Medical management of pain and symptoms is a major principle of cachexia management. Cancer patients are subject to many discrete and potentially reversible causes of reduced food intake and weight loss which must be assessed and appropriately managed. Causes of weight loss that are amenable to effective management are legion (see Box 10.2), e.g. pain, nausea, vomiting, dental problems, dysphagia, early satiety, intestinal motility disorders, oesophageal obstruction, malabsorption, endocrine and metabolic disorders, anxiety, depression, distress, and inability to sleep. These issues should be treated according to clinical practice guidelines for pain and symptom management. One must use a systematic approach to pinpoint these contributory factors (see Box 10.2); each must be identified as they may respond to therapies unique unto themselves.

Box 10.2 Potentially correctable causes of cancer anorexia–cachexia

Psychological factors

- Anxiety
- Depression
- Family distress
- Spiritual distress
- Social isolation

Eating problems

- Disturbed taste or smell

Oral

- Dentures
- Mouth sores
- Thrush
- Dry mouth

Swallowing difficulty

Stomach

- Gastric reflux
- Early satiety
- Nausea and vomiting

Bowel

- Obstruction
- Constipation
- Diarrhoea

Malabsorption

- Pancreas
- Fistulae

Fatigue

- Sleep disturbances
- Motivation
- Cognitive fatigue

Box 10.2 *(continued)*

Function

- Physical limitation

Pain

Metabolic

- Diabetes
- Adrenal insufficiency
- Hypogonadism
- Thyroid insufficiency
- Low testosterone

Question 4. Are some cancers more likely than others to cause cachexia?

Patients with cancer of the pancreas and lung and upper gastrointestinal tumours commonly present with weight loss.[3] For unknown reasons, wasting is unusual in breast and haematologic cancers at onset of the disease. Other tumours hold an intermediate position. Anorexia–cachexia is often a final common pathway encountered prior to death in all cancers, congestive heart failure, COPD, renal failure, and other chronic fatal disorders.

The time of onset of anorexia–cachexia shows a large degree of intra-individual variation among persons with the same type of cancer, preceding the diagnosis in some cases, and appearing during treatment or at later stages of disease in others.

Question 5. How do patients and families experience anorexia–cachexia?

Patients with cachexia and their family members may suffer from profound psychosocial distress, yet this is less well explored than the biomedical aspects of the condition. The distress encompasses a myriad of intersecting factors, including patients' and family members' struggles to cope, disturbance of relationships, and changing roles.[6,7,8] It is important to be aware that the experience of anorexia–cachexia by patients and families occurs within unique personal, social, historical, and cultural contexts.

Patients and families express distress about weight loss, altered body image, and inability to eat and are mindful that severe weight loss foreshadows death.[9] The wasted appearance of the cachectic patient with cancer is a major source of concern for both patients and families. If asked, they will describe laborious efforts to maintain and increase food intake.

A lack of control over weight loss is frustrating; even the most successful therapies only slow it down. Fatigue, weakness, and loss of independence compound the sense of loss of control in patients, as does feeling pressured by others to eat more food. If the patient and his or her family members do not have an equal degree of understanding of the disruption in food connections, conflict with family members over food and social isolation can ensue.[6] For patients, the inability

to share food in the manner hoped for by family members can contribute to a larger concern about being a burden.[6]

Case 10.1 (continued)

C.L. and her immediate family were understandably shocked when informed of the diagnosis and illness prognosis. They, with her mother (father deceased), are a highly supportive group, bolstered by relatives and friends. They adopted a philosophy of 'prepare for the worst, but accept the best' and buckled down to both try to control the cancer and enjoy life, expecting better control of the anorexia–cachexia syndrome. The patient accepted the invitation to take part in a clinical trial of chemotherapeutic agents. The acute pain subsided and was controlled with low-dose opioid therapy.

Question 6. How should we assess C.L.'s anorexia–cachexia?

The philosophy of identifying problems early in the trajectory of a chronic illness and introducing palliative care principles at this time is now generally accepted; so it is for anorexia–cachexia. We emphasize that early identification and therapy are an ideal to be approached, dependent on the setting, resources, and time of patient contact. Early or late, however, and dependent on the physician's judgement, the principles remain the same. The care of patients with anorexia–cachexia must seamlessly integrate with the overall coordinated oncology–palliative care treatment plan.

Specific elements essential for an anorexia–cachexia assessment include:

1. Initial weight and height obtained in a standardized fashion, that is:
   - No shoes or outer garments.
   - Reliable scale which will also be used for follow-up.
   - Empty pockets.
   - Note presence of pleural effusion, ascites, or oedema.
   - Note last bowel movement.
   - Height information, coupled with weight history, will enable calculation of the BMI (kg/m^2) and the weight loss grade[1] (see Figure 10.1). At presentation, C.L. has experienced Grade 3 weight loss prior to starting any therapy. It is critically important to chart on return visits changes in weight and BMI. Weight loss grades are independently prognostic of mortality and this should inform decisions on the risk/benefit of therapeutic alternatives and patient/family considerations.
2. Patient-recorded information is important, and simple questionnaires in the office or clinic will help get to the heart of the matter:
   - History of weight loss during last 6 months.
   - The revised Edmonton Symptom Assessment Scale (ESASr) is a helpful symptom checklist.[10]
   - Patient-Generated Subjective Global Assessment (PG-SGA). This questionnaire scores patient-reported food intake, weight loss, and symptoms impacting on food intake, together with patient estimation of function.[11]
   - Distress thermometer (provides patient reports on psychosocial issues which influence anorexia–cachexia, well as on other symptoms and sources of social distress relevant to overall care).[12]

For a more in-depth review of concerns, validated tools for assessment of quality of life (QOL) may be used. The European Organization for Research and Treatment of Cancer QLQ-CAX24 is a cancer cachexia-specific questionnaire comprising five multi-item scales (food aversion, eating and weight loss worry, eating difficulties, loss of control, and physical decline).[13] The Functional Assessment of Anorexia Cachexia Therapy (FAACT) questionnaire has a 12-point anorexia–cachexia subscale.[14]

Muscle mass and function

Muscle loss is obvious in the clinically underweight patient. Detection of muscle loss in obese patients is challenging; however, specialty clinics are emerging, equipped with radiologic techniques (dual-energy X-ray or computed tomography) to accurately assess muscle loss.[15] These patients do not look thin or underweight but will still have fatigue, muscle weakness, and other symptoms associated with cachexia, together with altered responses to therapy.[3]

In any clinic, simple tests of function should be employed. Note the patient's ability to walk over a timed period (e.g. 2 or 6 minutes) and inquire about activities at home. Physiotherapists can quantify static function using the following assessment tests:

- Six-minute walk.
- Sit-to-stand timing.
- Gait speed.

Dynamic function over time can be assessed with the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire.[16] Occupational therapists can assess the patient's ability to function at home and in public.

Some specialty clinics are now using patient-friendly devices (activity monitors) which measure the actual amount of walking, other movements, and sedentary time.

Biological criteria

Standard laboratory tests can alert to the presence of an inflammatory state. The acute phase protein CRP is readily tested. Increases in CRP strongly correlate with severity of cachexia and bode a bad prognosis across a range of cancers.[17] An increase in neutrophils with a decrease in lymphocytes also is a sentinel for a chronic inflammatory state.

Question 7. What is the framework for an anorexia–cachexia therapeutic platform?

Decide on which of the potential elements of cachexia are evident (usually this includes tumour- and treatment-related effects, symptoms, and psychosocial factors). Box 10.2 outlines a checklist which may be used. Aggressively treat all identified potentially modifiable issues.

1. Make full use of the team available. Key components include, in addition to the usual palliative care team, a registered dietitian, a physical therapist, an occupational therapist, a psychologist, and a social worker.
2. Family members are particularly motivated to support their loved ones. Enlist them as active members of the team. Nutrition and rehabilitation are approaches readily understood by families—these are their therapies, while professionals serve as advisors. This opportunity for an active care role is greatly appreciated by them.
3. Employ specific protocols for assessment and treatment.

Case 10.1 (continued)

C.L. and her family enthusiastically accepted their team role. They had helpful ideas, based on their past experience and culture which they now felt empowered to discuss with the care team. Some involved complementary therapies, but most involved techniques for enhancing food intake.

Question 8. What general dietary advice will you employ when the patient has a good performance status?

Inadequate dietary intake is endemic in patients with advanced cancer and thus, provision of adequate nutrition is a mainstay of treatment.[2,3,18]

1. Access key expertise.
   - Evidence-based guidelines for clinical nutrition in oncology are a strong primary resource.[18] Counselling by a registered dietitian aims to provide patients with a thorough understanding of nutritional issues that can lead to lasting changes in eating habits. Gastroenterologist consultation may be relevant in instances where patients are unable to eat, digest, or absorb food and procedures such as stent or artificial feeding may be required.
2. Create awareness of potentially harmful diets.
   - Discourage use of supplements and diets that are not based on clinical evidence and that potentially could be harmful. Specific harms may include secondary micronutrient deficiency, exacerbation of malnutrition, and high cost. There are no diets known to reproducibly cure cancer or prevent cancer recurrence.
3. Basic nutritional requirements for macronutrients and micronutrients.
   - Energy and lipids:[18]
     - Total energy expenditure of cancer patients may be assumed to range between 25 and 30 kcal/kg body weight/day.
     - Increase the energy density of the diet, that is increase the ratio of energy from fat to energy from carbohydrates.
   - Protein and amino acids:[18]
     - Protein intake should be 1–1.5 g/kg body weight/day.
     - The primary source can be good-quality protein from meat, fish, eggs, dairy products, and/or plant sources, as tolerated.
     - There are insufficient consistent clinical data to recommend supplementation with purified amino acids. Protein-rich dietary supplements (e.g. whey) may be helpful.
   - Micronutrients:
     - Vitamins and minerals should be supplied in amounts approximately equal to the recommended daily allowance for adults.[18] Note that patients on poor diets and with little sun exposure are at particular risk of vitamin D deficiency.
     - Discourage the use of high-dose micronutrients in the absence of specific deficiencies.
     - Antioxidant effects of some vitamins may interfere with some cancer therapies. Therefore, it is prudent to withhold them during an active chemo-radiotherapy phase.
4. Exercise in combination with nutrition.
   - Current oncology nutrition clinical practice guidelines recommend maintenance or an increased level of physical activity in cancer patients to support muscle mass and physical function and sustain insulin sensitivity.[18]

5. Options and tips for meals:
   - Altered taste and smell, nausea, and the development of food aversion are commonly experienced by patients and profoundly affect food intake and food enjoyment. Some helpful practice may include:
     - Experiment with various spices and flavourings (e.g. lemon, orange, or fruit juices, pickles, chutney, marinades, and sauces). Plain milk may be more palatable if fruit or chocolate syrups are added.
     - Avoid or mask unpleasant odours or tastes. The addition of sugar to foods and taking sparkling water prior to eating may reduce bitter or metallic tastes. Freshen mouth with fruit drops or cleanse mouth between meals with soda water or baking soda. If patients find odours problematic, ensure that cooking is done elsewhere, serve food in an atmosphere free of odours, and serve dishes that are eaten cold.
     - Be attentive to food presentation and atmosphere during meals. Vary colour and use garnishes. Use attractive tableware, with music as background. A little beer, wine, or spirits may help, if one is in the custom of enjoying them with meals. Limit alcohol during chemotherapy.
     - Portions, meal size, and meal frequency. Serve small portions, as large amounts can discourage a patient. You can always give a second helping or encourage snacks during the day. Patients may prefer to take small meals frequently—up to 5–6 daily. Mealtimes are social events. This should not change; eat with family and friends; however, care must be taken not to force food or make patients feel guilty for not eating.

Question 9. Are there specific dietary supplements which can be used?

1. Oral nutritional supplements are sterile liquids, semi-solids, or powders that are usually nutritionally complete mixtures intended to supplement volitional food intake. Supplements may be helpful; however, their use should complement, not replace, regular food intake. Some trial and error efforts are needed to plan supplement use, so that it does not supplant meals.
2. Supplementation with long-chain polyunsaturated omega-3 fatty acids may stabilize or improve appetite, food intake, lean body mass, and body weight.[18]

The specific elements are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are found in fatty marine fish (e.g. salmon, sardine, mackerel) and their oils. Doses are in the range of 2.0–2.5 g/day total EPA + DHA; these are available as purified fish oil concentrates. Omega-3 fatty acids reduce formation of pro-inflammatory eicosanoids and may have other less clearly identified effects. Toxicity is modest—they can reduce platelet aggregation and could increase bleeding risks in patients with major thrombocytopenic risk or at risk of bleeding from other causes.

Case 10.1 (continued)

C.L.'s past activities included daily running and regular participation in a yoga group. She asked if it was safe for her to continue this practice. She received an enthusiastic 'yes' from the team.

Question 10. Is exercise helpful for patients with a good performance status?

According to their capability and safety profile, patients should be offered an exercise programme, in combination with nutrition support. Exercise is a non-pharmacologic therapy where the patient is in charge, thus consolidating their recognition that they are active team members.

It is recommended to maintain or increase the level of physical activity in cancer patients to support muscle mass, physical function, and psychosocial well-being.[18] Data from published trials provide strong evidence that physical activity is well tolerated and safe at different stages of cancer, and also that patients with advanced stages of disease are able and willing to engage in physical activity.[19,20]

Case 10.1 (continued)

In addition to dietary counselling, vitamin D, omega-3 fatty acids (in the form of fish oil), and an exercise programme were initiated. C.L. had prior experience with yoga, which she was advised to continue, while she adopted a mixed cardiovascular resistance exercise routine.

The family asked whether more specific therapies to improve appetite or build muscle should be employed.

Question 11. Are there any proven drugs which control anorexia–cachexia?

There are agents which enhance appetite. To date, no approved agents improve muscle mass or function. A comprehensive review of individual trials appeared in 2015.[21]

Appetite stimulants

Corticosteroids

They are powerful appetite enhancers; unfortunately, they also increase muscle breakdown. Their action probably relates to anti-inflammation, although specific mechanisms are uncertain.

Because they cause reduced muscle mass, corticosteroids are not suitable for long-term use. They are helpful in short-term courses to boost appetite or towards the end of life to assist patients whose mobility is such that improving appetite trumps attempts to maintain walking. Methylprednisolone mitigates pain, fatigue, and appetite loss in patients with advanced cancer using opioids.[22]

Fluorinated corticosteroids such as dexamethasone are potent inducers of muscle catabolism . Therefore, prednisone or its congeners are safer choices, although they are more likely to cause fluid–electrolyte changes.

Progestational agents The most commonly employed is megestrol acetate, clearly demonstrated in many high-quality studies to increase appetite.[21] Weight gain follows—almost completely due to fat accumulation. Studies in geriatric populations concluded that progestational agents had a catabolic effect on muscle, perhaps in part because of their anti-androgenic actions. We still recommend that megestrol be used in short-term courses to improve appetite in physically active patients; if sedentary, longer courses may be used. Due to its cost, some patients cannot obtain this.

Thromboembolism is the principal associated risk, although this outcome is modest in patients without past or current thromboembolic disorder.

Cannabinoids Often a strong orexigenic effect is obtained in healthy people (the 'munchies'), in some part due to their ability to enhance taste and smell, thus increasing food palatability. Their actions probably stem from their modulation of central cerebral–hypothalamic pathways, although they have protean peripheral effects; cannabinoid receptors are widespread throughout the body.

Because of social connotations, their medical use has been constrained, both in research and practice. Evidence for success in clinical studies is mixed. We believe they may be helpful in those patients bothered by appetite–taste–smell aberrations,[23] with a low risk level of unwanted mental changes, that is people with delirium/dementia or deemed to be dementia candidates, although in most studies, at standard doses of oral cannabinoids, this risk is low. A side benefit of improved sleep may be noted.

Most research has been on oral compounds. It is not known whether alternate routes (e.g. smoking, aerosols) are superior. Cannabinoid oral pharmacokinetics are complex and palliative care patients may have varying changes in drug metabolism. New research should explore these avenues. To date, it is not possible to recommend specific dosages of the various available cannabinoids.

(See Chapter 33 on cannabinoids.)

Anabolic steroids Many cancer patients are hypogonadal, particularly if they are elderly and/or on opioids.[24] Low testosterone logically may be accompanied by reduced muscle synthesis. Although there is supportive evidence in the geriatric literature, evidence for replacement therapy in patients with cancer is lacking.

Replacement (physiologic, not pharmacologic, dosage) testosterone may be used in wasted, hypogonadal patients after detailed discussion regarding adverse effects, for example sexuality—not every sick elderly person welcomes an increased libido once the fires are banked.

Gastric stimulants and laxatives

While not classic anti-anorexia–cachexia agents, they are part of an overall drug platform. Appetite is destroyed in patients with severe constipation. One must adhere to a religious bowel care routine (see Chapter 8 on constipation); assessment is critical for patients both on or off laxatives.

Widespread aberrations in autonomic control systems are noted in cancer patients; they contribute to the delayed gastric emptying commonly observed. This contributes to poor appetite and nourishment; however, there are probably different dysmotility syndromes—will gastric stimulants work in this complex setting? A few small studies support the use of metoclopramide.[25] While awaiting further enlightenment, it is reasonable practice to offer patients a short trial of metoclopramide when symptoms (rapid satiety, bloating) are present. It has a variety of adverse effects. In particular, there is a risk of cardiac arrhythmias. Thus, it must be used with caution in patients with cardiac disease or evidence of a short QT interval on the electrocardiogram (ECG). Follow-up ECG monitoring is recommended.

Case 10.1 (continued)

C.L. was placed on a laxative protocol and metoclopramide. She tried her son's marijuana, with consequent improvement in sleep and enjoyment of food. Whether this happy outcome stemmed from the marijuana or her short-lived tumour response on chemotherapy is open to question. Over the next 4 months, C.L. gained back her weight, returned to near-normal activity, and enjoyed excellent symptom control.

Evidence from a CT scan of tumour relapse was accompanied by an increase in pain and loss of appetite with weight loss. Her fatigue scores remained satisfactory. She refused further chemotherapy and enrolled in a cachexia drug trial. She also had a coeliac plexus bloc, with good effect.

Appetite returned, as did her weight, while her activity levels remained near normal. Distress scores were low. Once again, she was bolstered by her strong family who were actively involved in care and by the palliative care team who readily segued the prime focus of care towards control of anorexia–cachexia and associated symptoms.

The pancreatic cancer grew apace. Six weeks later, despite all efforts, all manifestations of anorexia–cachexia returned. She had a dramatic decrease in food intake, and her weight and activity levels plummeted. The family were distressed (the patient less so) with these devastating changes. One relative strongly campaigned for the use of parenteral feeding.

Question 12. Is there a role for enteral–parenteral therapy?

Here we consider therapies with substantive ethical overlays. It is an act of human kindness to feed another who is wasting; often families believe this is one of the last sources of solace they offer a loved one. Sometimes their concerns lead to demands for artificial means of feeding.

Certainly, in cancer patients who are severely malnourished as a result of aggressive therapy, or are expected to be so at surgery, there is an established role. Benefits are less apparent in advanced cancer patients and it has been suggested that anorexia–cachexia culminates in a refractory stage.[2] Oncology nutrition clinical practice guidelines[18] recommend offering and implementing nutritional interventions in patients with advanced cancer only after considering, together with the patient, the prognosis of the malignant disease and the expected benefit on both QOL and potentially survival, as well as the burden associated with this form of nutritional care. Prognostication of survival is considered essential to the decision-making process; if expected survival is in the range of 1–3 months, interventions should be non-invasive and primarily aimed at symptom control, as well as psychosocial and existential support. Patients with a comparably good prognosis and an expected overall survival of at least 3 months, as well as patients with low tumour activity and low inflammation (CRP <10 mg/dl), should receive adequate nutritional counselling and support, including oral or enteral feeding, in the first instance, or, if required, parenteral nutrition or combinations.

The use of artificial nutrition in the care of patients with cancer has divergent local variations, ranging from being considered the standard of care to rare or infrequent use; this variation is often religious or cultural. The expectations and wishes of the patient and close relatives or partners should be taken into consideration, and taken in context of their understanding of the illness, preparation for end of life, and caring around the dying process, as well as spiritual concerns. Psychosocial support to patients and families is particularly relevant in the far-advanced disease stage when the patient is no longer eating and artificial nutritional support is not indicated.[26] The components of such support include a reduced emphasis on preparing and serving food, enabling the family to provide aid without applying pressure, and providing information about anorexia–cachexia and how it will affect the patient and their families.

Case 10.1 (continued)

After thorough discussion, all agreed that enteral–parenteral feeding was not advisable. C.L. had massive liver metastases and her survival with pancreatic cancer was estimated to be in the range of 3–12 weeks. The odds on improving her life quality with artificial nutrition were deemed to be vanishingly small.

The patient received a short course of prednisolone, with a positive appetite effect. C.L. was switched to megestrol, which may have slowed weight loss and helped maintain food intake.

Fatigue became a major feature. Occupational therapy advice throughout her course had been helpful; now the occupational and physiotherapy team members concentrated on safe conservation of strength and maintenance of home-based activities.

Illness progression continued, but C.L. remained at home in good pain control, without psychosocial distress. She died at home surrounded by family; her exit was dignified and peaceful.

Question 13. Are there promising research trends?

Our expanding understanding of the biological underpinnings of cachexia is reflected in ongoing trials of new drugs.

Growth hormone secretagogue receptor type 1 (ghrelin receptor) agonists

These are new therapies to increase food intake. Ghrelin is a hormone primarily secreted by the stomach which induces growth hormone activity. Hunger stimulates its release and its subsequent orexigenic effects are mediated by receptors in the CNS. Results are available for Anamorelin®, including Phase III clinical trials demonstrating gain of weight and lean tissue and improved QOL.[27] NCT03743064, and this agent was approved for therapeutic use in Japan in 2021. Further Phase III investigation of this agent, is under way.

Melanocortin receptor 4 antagonists

These agents act on the hypothalamus, which regulates appetite and satiety but also have systemic effects to promote protein anabolism and energy storage. Selective inhibition of MC-4R in animal systems reduce all elements of cachexia. Human trials are awaited.

Modifiers of autonomic function

Through its combined pharmacological actions, the β-blocker espindolol (the s-isomer of the better known pindolol) has a multifunctional effect upon three potential pharmacological targets, including: (1) reduced catabolism by non-selective β receptor blockade; (2) reduced fatigue and thermogenesis, through central 5HT1a receptor antagonism; (3) and increased anabolism through partial β2 receptor agonism. Promising preliminary results were obtained with espindolol.[28]

Multimodal therapy

As emphasized previously, multimodal cachexia therapy is achieved by a collaborative approach that engages a multidisciplinary team of health professionals, as well as patients and their families. This process will be further illuminated by an international study—including three Canadian cancer centres—now under way. NCT02330926—Multimodal Intervention for Cachexia in Advanced Cancer Patients Undergoing Chemotherapy (the MENAC study[29]—combines nutrition and exercise with anti-inflammatory drugs (ibuprofen and omega-3 fatty acids). We are convinced that major advances will depend upon an approach which addresses the inherent complexity of anorexia–cachexia and embodies 'whole person care'.

Primacy of cachexia trials

To date, trial participants have often been far along in their illness trajectory. They have marked wasting and often drop out from the study. It is key to combat cachexia early—yet there are many

obstacles to enrolling participants at the time when they may experience a successful outcome; the ethical issues relevant to this dilemma must be resolved.[30]

Conclusion

Anorexia–cachexia is a highly complex and, as of yet, not fully understood condition. Thorough assessment of the patient, including the impact of the condition on both the patient and loved ones, is important. There are many potential treatments, dependent upon the goals of care and the patient's performance status. Research is ongoing.

References

1. **Martin L, Senesse P, Gioulbasanis I** *et al.* (2015) Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol*, **33**(1), 90–9.
2. **Fearon K, Strasser F, Anker SD** *et al.* (2011) Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*, **12**(5), 489–95.
3. **Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH** (2018) Cancer-associated cachexia. *Nat Rev Dis Primers*, **4**, 17105.
4. **Campos CA, Bowen AJ, Han S, Wisse BE, Palmiter RD, Schwartz MW** (2017) Cancer-induced anorexia and malaise are mediated by CGRP neurons in the parabrachial nucleus. *Nat Neurosci*, **20**(7), 934–42.
5. **Schiessel DL, Baracos VE** (2018) Barriers to cancer nutrition therapy: excess catabolism of muscle and adipose tissues induced by tumour products and chemotherapy. *Proc Nutr Soc*, **77**(4), 394–402.
6. **Hopkinson JB** (2014) Psychosocial impact of cancer cachexia. *J Cachexia Sarcopenia Muscle*, **5**, 89–94.
7. **Wheelwright S**, **Darlington AS**, **Hopkinson JB** *et al.* (2013) A systematic review of health-related quality of life instruments in patients with cancer cachexia. *Support Care Cancer*, **21**, 2625–36.
8. **Oberholzer R**, **Hopkinson JB**, **Baumann K** *et al.* (2013) Psychosocial effects of cancer cachexia: a systematic literature search and qualitative analysis. *J Pain Symptom Manage*, **46**, 77–95.
9. **Shragge JE, Wismer WV**, **Olson KL**, **Baracos VE** (2007) Shifting to conscious control: psychosocial and dietary management of anorexia by patients with advanced cancer. *Palliat Med*, **21**, 227–33.
10. **Watanabe SM, Nekolaichuk C, Beaumont C,** *et al.* (2012) A multi-centre validation study of two numerical versions of the Edmonton Symptom Assessment System in palliative care patients. *J Pain Symptom Manage*, **21**(9), 977–85.
11. **Ottery FD** (1996) Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition*, **12**(1Suppl), S15–19.
12. **Tuinman MA, Gazendam-Donofrio SM, Hoekstra Weebers JE** (2008) Screening and referral for psychosocial distress in oncologic practice: use of the distress thermometer. *Cancer*, **113**(4), 870–8.
13. **Wheelwright SJ**, **Hopkinson JB**, **Darlington AS**, *et al.* (2017) Development of the EORTC QLQ-CAX24, a questionnaire for cancer patients with cachexia. *J Pain Symptom Manage*, **53**, 232–42.
14. **Gelhorn HL, Gries KS, Speck RM** *et al.* (2019) Comprehensive validation of the functional assessment of anorexia/cachexia therapy (FAACT) anorexia/cachexia subscale (A/CS) in lung cancer patients with involuntary weight loss. *Qual Life Res*, **28**(6), 1641–53.
15. **Martin L, Birdsell L, Macdonald N** *et al.* (2013) Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol*, **31**(12), 1539–47.
16. **Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, Ritter PL** (2001) CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med Sci Sports Exerc*, **33**(7), 1126–41.

17. **Dolan RD**, **McSorley ST**, **Horgan PG**, **Laird B**, **McMillan DC** (2017) The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: systematic review and meta-analysis. *Crit Rev Oncol Hematol*, **116**, 134–46.
18. **Arends J, Bachmann P, Baracos V** *et al.* (2017) ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*, **36**(1), 11–48.
19. **Oldervoll LM, Loge JH, Lydersen S** *et al.* (2011) Physical exercise for cancer patients with advanced disease: a randomized controlled trial. *Oncology*, **16**, 1649e57.
20. **Hall CC, Cook J, Maddocks M, Skipworth RJE, Fallon M, Laird BJ** (2019) Combined exercise and nutritional rehabilitation in outpatients with incurable cancer: a systematic review. *Support Care Cancer*, **27**(7), 2371–84.
21. **Baracos VE, Watanabe S, Fearon K** (2015) Aetiology, classification, assessment and treatment of anorexia–cachexia syndrome. In: Cherney N (ed.) *The Oxford Textbook of Palliative Medicine*, 5th edn, pp. 702–12. Oxford University Press, Oxford.
22. **Paulsen O, Klepstad P, Rosland JH** *et al.* (2014) Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. *J Clin Oncol*, **32**(29), 3221–8.
23. **Brisbois TD, de Kock IH, Watanabe SM** *et al.* (2011) Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol*, **22**(9), 2086–93.
24. **Skipworth RJ, Moses AG, Sangster K** *et al.* (2011) Interaction of gonadal status with systemic inflammation and opioid use in determining nutritional status and prognosis in advanced pancreatic cancer. *Support Care Cancer*, **19**(3), 391–401.
25. **Malik JS, Yennurajalingam S** (2019) Prokinetics and ghrelin for the management of cancer cachexia syndrome. *Ann Palliat Med*, **8**(1), 80–5.
26. **Maddocks M**, **Hopkinson J**, **Conibear J** *et al.* (2016) Practical multimodal care for cancer cachexia. *Curr Opin Support Palliat Care*, **10**, 298–305.
27. **Temel JS**, **Abernethy AP**, **Currow DC** *et al.* (2016) Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *Lancet Oncol*, **17**(4), 519–31.
28. **Stewart Coats AJ, Ho GF, Prabhash K** *et al.*; **for and on behalf of the ACT-ONE Study Group** (2016) Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomized, double-blind, placebo-controlled, international multicentre phase II study (the ACT-ONE trial). *J Cachexia Sarcopenia Muscle*, **7**(3), 355–65.
29. **Solheim TS, Laird BJA, Balstad TR** *et al.* (2018) Cancer cachexia: rationale for the MENAC (Multimodal-Exercise, Nutrition and Anti-inflammatory medication for Cachexia) trial. *BMJ Support Palliat Care*, **8**(3), 258–65.
30. **MacDonald N** (2013) Multimodal cancer care research. *Curr Oncol*, **20**(6), 298–300.

Chapter 11

Cancer fatigue

Ravi Bhargava and Martin Chasen

Attitude

To enable each learner to:

- Reflect on the complexity of symptoms that patients with cancer experience, specifically fatigue.
- Understand how cancer-related fatigue (CRF) and its treatment impact the patient's overall physical, emotional, psychosocial, and functional states.

Skills

To enable each learner to:

- Understand and assess the components of fatigue while recognizing the simultaneously occurring symptoms of pain and depression.
- Formulate management plans that include selecting the appropriate pharmacological treatments, physical activity and exercise prescriptions, and psychosocial and other integrative interventions.
- Demonstrate a patient-centred approach to managing CRF that recognizes the patient's goals of care.

Knowledge

To enable the learner to:

- Describe the screening, assessment, evaluation, and different treatment strategies for the management of CRF and its associated symptoms.
- Review the multidimensional components and pathophysiology of CRF.
- Recognize the cancer trajectory with the associated physical and functional effects encountered by patients.
- Recognize the role of physical activity and exercise in the management of CRF.

Case 11.1

N.M. is a 68-year-old married woman. One month prior to her diagnosis of gall bladder cancer, she experienced increasing abdominal pain, loss of appetite, nausea, and a 10-kg weight loss.

At first visit, she reported to the palliative care team that she had a lack of 'energy' and was unable to enjoy prolonged physical activity. This fatigue had started prior to the diagnosis and had progressively worsened. She also complained of poor appetite, an absence of taste, early satiety, excessive flatulence, weight loss, and

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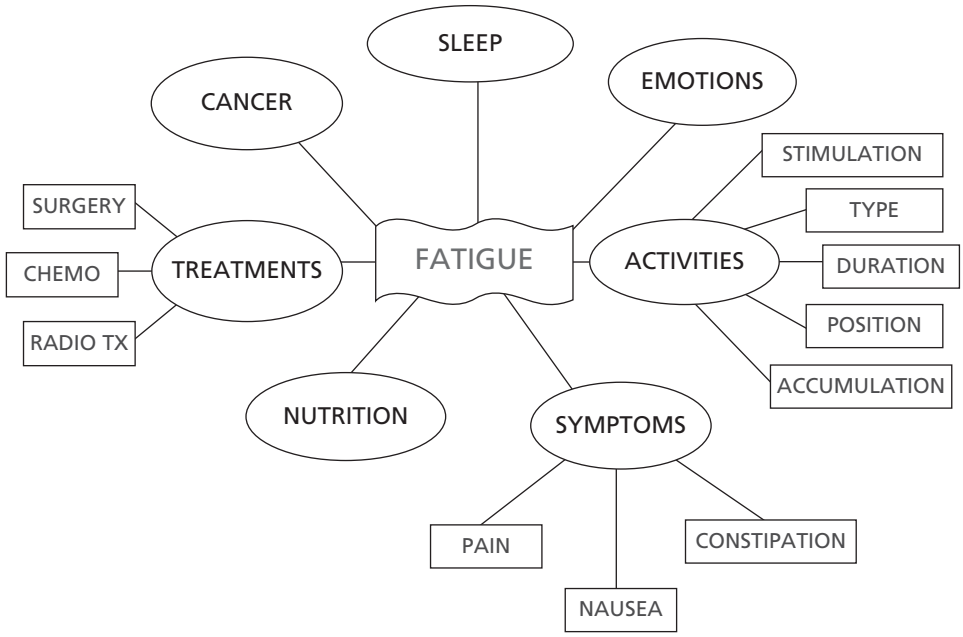


Fig. 11.1 Multidimensional components of fatigue.
Source: data from Olson K, et al. 'Possible links between behavioural and physiological indices of tiredness, fatigue, and exhaustion in advanced cancer'. *Supportive Care in Cancer*, Vol. 16, Issue 3, pp. 241–249. © 2008 Springer Nature.

continuous abdominal pain. She was also distressed by insomnia, decreased ability to concentrate, and low mood and anxiety, particularly concerning her future.

Question 1. What is cancer-related fatigue?

CRF has been reported as one of cancer's most distressing symptoms.[6] Over 70% of patients with cancer experience fatigue.[7] CRF is defined as a persistent, subjective sense of physical, emotional, and/or cognitive tiredness related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.[6] CRF can compromise the dosing and timing of treatments, thereby affecting treatment adherence and survival. Despite its prevalence and negative impact, the diagnosis of CRF is often missed.[6]

Factors contributing to CRF are multifactorial (see Figure 11.1).[8]

Components of CRF include general, physical, emotional, and mental fatigue. CRF is differentiated from other types of fatigue by its severity, persistence, and the inability to alleviate it through rest. Increasing effectiveness of adjuvant therapies has resulted in an ever increasing number of cancer survivors. However, many survivors experience long-term adverse effects from previous treatments, which deteriorate health-related quality of life (HRQOL).

Changes associated with CRF include:

- Decreased cognitive function.
- Decreased muscle endurance.

- Decreased sleep quality.
- Decreased control over body processes.
- Increased social withdrawal.
- Increased emotional reactivity.

Question 2. What is the pathophysiology of cancer-related fatigue?

The specific mechanisms involved in the pathophysiology of CRF are unknown. Proposed mechanisms include pro-inflammatory cytokines, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, circadian rhythm desynchronization, and skeletal muscle fatigue, especially in cancer survivors with no evidence of active disease, and some have suggested that persistent immune system activation and chronic inflammatory processes may be involved.[9] Evidence supporting these mechanisms is limited.

CRF may be caused by:

1. Pain.
2. Symptoms related to energy imbalance (i.e. anaemia, cachexia, infection, paraneoplastic syndromes, and metabolic disorders).
3. Treatments (i.e. stress, mood, and fatigue induced by cancer therapies or by agents used for pain relief).

The most widely accepted hypothesis has been attributed to energy imbalance. Anaemia, a sequela of cancer or its treatment, leads to tissue hypoperfusion and a negative net energy balance. Pro-inflammatory cytokines induce cachexia and fatigue; hence, a chronic inflammatory state (CIS) results in fatigue.

Chronic physiological stress can contribute to fatigue by activating the HPA axis, which is the central regulatory system governing the release of the stress hormone cortisol. Hyperactivity of the HPA axis can lead to depression, enhancing fatigue.

The role of cardiac or pulmonary dysfunction in CRF has not been studied. It may, however, play a role in some patients, notably those treated with cardiotoxic drugs or who have cancer cachexia. The possible role of psychological disorders in CRF is also unclear. Descriptive studies show that fatigue rarely occurs in isolation, usually being associated with pain, insomnia, and sleep disturbance. While the inciting factors may not be clear, usually activity loss associated with fatigue accentuates the problem, causing a negative feedback loop. This reinforces the importance of prescribing exercise therapy.

Question 3. How do you assess fatigue?

Fatigue is a subjective experience. Clinicians must rely on their patients' descriptions of the level of fatigue they are experiencing. It is prudent to screen for common contributing factors, in addition to medical conditions, such as emotional distress, sleep disturbance, pain, and use of prescription drugs or over-the-counter medications or supplements. The best way to measure fatigue is to use self-reported measures. The National Comprehensive Cancer Network (NCCN) recommends the use of a single-item, 11-point, numerical rating scale as a screening tool for CRF.[10] The NCCN guidelines recommend that patients with a score of 0–3 fall under 'none to mild' fatigue, and patients with scores of 4–6 or 7–10 fall under 'moderate' to 'severe' fatigue, respectively. When

fatigue is rated as moderate to severe, a more focused history and physical examination should be conducted. A thorough history is warranted, because the recommended work-up for fatigue differs according to the timing of fatigue onset in relation to the completion of active therapy and the presence of predisposing factors and other symptoms.

Uni-dimensional scales measure the severity of fatigue. A good example is the Functional Assessment of Cancer Therapy–Fatigue (FACT-F) scale.[11] The FACT-F includes a brief 13-item fatigue subscale that has been used to detect clinically meaningful differences in fatigue scores in response to treatment.

The Multi-dimensional Fatigue Inventory (MFI) has been validated in patients with cancer and focuses on the subjective experience of fatigue.[12] This scale evaluates the general, mental, and physical dimensions of fatigue, as well as levels of motivation and activity. The 20-item version of the MFI is used to assess fatigue in patients with a variety of cancers who are receiving chemotherapy or radiotherapy. The MFI can also capture differences in CRF across time. Using this scale, higher levels of fatigue have been detected during and immediately after treatment. It has also been used to demonstrate the persistence of multiple dimensions of fatigue after completion of initial treatment in a range of cancers.

Regardless of the onset of fatigue, screening for common contributing factors, such as emotional distress, sleep disturbance, pain, and use of prescription drugs or over-the-counter medications or supplements should always be considered.

Screening for fatigue

All patients with cancer should be screened for fatigue to ensure that those with moderate to severe fatigue are identified and treated promptly and effectively. According to the fatigue severity scale, patients should be asked, 'How would you rate your fatigue on a scale of 0 to 10 over the past 7 days?' Alternately, screening can be performed with patients asked to rate their fatigue as none, mild, moderate, or severe. Scores of 0–3 or none to mild fatigue require no further assessment or interventions; these patients should be rescreened at regular intervals. Patients with scores of 4 or greater or indicating moderate or severe fatigue should be evaluated further. Studies in patients with cancer have revealed a marked decrease in physical functioning at a reported fatigue level of 7 or higher on the 0 to 10 scale of the Brief Fatigue Inventory (BFI).[3]

Case 11.1 (continued)

N.M was fully evaluated for her fatigue. In addition to the history and physical examination, allied health evaluations were sought. The BFI showed that the fatigue level was 8 or higher in all the parameters assessed in the questionnaire. Her Distress Thermometer (DT)[4] was 5, and the reasons recorded were: tiredness, pain, depression, and difficulty in explaining her current emotional and functional problems to her husband.

The physiotherapy assessment documented poor posture, with decreased strength and muscle mass. The result of the 6-minute walk test was 305 m and sit to stand was 12 seconds. Her leg stand test was 5.2 seconds on the left and 4.9 seconds on the right.

The occupational therapy assessment documented poor performance in her self-care activities of daily living (ADLs).[5] There was a lack of awareness of being able to pace herself or implement other energy-sparing techniques.

Both N.M. and her husband ask for help with her symptoms. In particular, her husband wants to know if exercise would be of benefit.

Question 4. How is fatigue managed?

Since fatigue is a complex multifactorial and multidimensional symptom, it is unlikely to be successfully managed with a single intervention. Treatment must always be tailored to the patient's disease and treatment status, preferences, and goals of treatment. An initial fatigue evaluation of all oncological patients should be considered, with all possible contributing factors identified and treated, prior to pharmacological and/or non-pharmacological CRF treatments being initiated.

Patients are likely to require a combination of integrative non-pharmacologic interventions, such as exercise, ergonomic advice, nutritional counselling, and correction of hormonal and metabolic abnormalities, as well as pharmacologic interventions aimed at mitigating the fatigue symptom complex.

Education and counselling

Education and counselling is recommended to help patients cope with fatigue. Physicians should set reasonable expectations regarding improvements in energy after completion of anti-cancer therapy to alleviate concerns of disease recurrence with remnant fatigue. Strategies for self-monitoring of fatigue and techniques, such as energy conservation, may be helpful in the immediate post-treatment period.[13]

Physical activity

Improving strength, energy, and fitness through even a moderate walking exercise programme has been shown to decrease anxiety and depression, improve body image, and increase tolerance for physical activity. Therefore, patients with moderate to severe fatigue should be encouraged to maintain adequate levels of physical activity. Robust data support the efficacy of increased physical activity in reducing fatigue in patients with cancer and cancer survivors.[14,15] A meta-analysis of 44 studies, including 3254 patients, concluded that moderate-intensity resistance exercise reduced CRF.[14]

Psychosocial intervention

Psychosocial intervention modalities to counter CRF include cognitive behavioural therapy, behavioural therapy, psychotherapy, support groups, changing coping strategies, relaxation, energy conservation, and stress management. Data from two meta-analyses on adult populations showed efficacy in reducing fatigue in adult cancer patients on active treatment.[16,17]

In an analysis of 41 studies with 3620 patients with cancer, Kangas *et al.*[16] showed significant effects of psychosocial interventions on fatigue. A meta-analysis by Duijts *et al.*[17] reported that, like exercise programmes, behavioural techniques, including cognitive therapy, relaxation techniques, counselling, social support, hypnosis, and biofeedback, are also beneficial in improving fatigue in patients with breast cancer.

Case 11.1 (continued)

N.M. has tried to be a bit more active daily, but as the weeks pass, she is finding it more problematic. She requires a rest mid morning and again in the afternoon. She is concerned that she will not have the energy to cope with a week-long visit with her grandchildren. She wants to be able to enjoy some fun activities with them during the week they are visiting. She wonders if there might be medication or a nutritional supplement that could help her.

Pharmacological treatments for CRF

Methylphenidate, a phenethylamine and piperidine class psycho-stimulant, has been evaluated for CRF in patients during and after cancer therapy. The meta-analysis included five studies showing significant reduction of CRF in 426 enrolled patients,[18] but heterogeneity among the studies affects the result. Nevertheless, the use of methylphenidate could be considered, since it begins acting quickly (24–48 hours after the start of treatment) and the treatment can be interrupted if response does not occur. Methylphenidate is a commonly considered treatment in palliative care.

Donepezil is a long-acting selective acetylcholinesterase inhibitor used for Alzheimer's disease. A double-blind, placebo-controlled trial in 142 patients with advanced cancer showed similarly improved fatigue and toxicity in both the donepezil and placebo groups.[19]

Paroxetine, a selective serotonin reuptake inhibitor, has shown no difference in the incidence or intensity of CRF in patients receiving chemotherapy. However, depression was significantly reduced in majority of these patient when compared with patients receiving placebo.[20]

Dexamethasone was studied in a double-blind, randomized, placebo-controlled trial in patients with advanced cancer; 84 elderly patients were enrolled.[21] A dose of 4 mg twice a day was effective in reducing fatigue, with a statistically significant improvement in Functional Assessment of Chronic Illness-Fatigue (FACIT-F) and Edmonton Symptom Assessment Scale (ESAS) scores.[2)]

Methylprednisolone was studied in a randomized, double-blind, placebo-controlled trial versus placebo on 50 advanced cancer patients using opioids (mean age in the methylprednisolone group was 62.5 years versus 66 years in the placebo group). Methylprednisolone 16 mg administered twice a day was superior to placebo in improving fatigue level and patient satisfaction.[22]

Non-pharmacological treatments

Nutraceutical interventions

A double-blind, randomized trial evaluated 2000 mg of *Wisconsin ginseng* (a common type of American ginseng) versus placebo for 8 weeks in 364 patients undergoing or having undergone curative intent treatment and showed a statistically significant difference at 8 weeks, especially in patients receiving active cancer treatment.[23]

L-carnitine supplementation has been studied in randomized trials in patients with advanced cancer and fatigue (mostly receiving radiotherapy or chemotherapy), without significant difference with respect to placebo, despite an increased serum level of carnitine.

Coenzyme Q10 showed no significant difference or only an initial difference (first 24 hours), compared to placebo, in a randomized study in women with breast cancer submitted to chemotherapy.[24,25]

In conclusions, methylphenidate and ginseng can be considered in patients with cancer during active oncological treatments for the treatment of CRF. However, evidence is weak and heterogeneous. Donepezil, paroxetine, L-carnitine, and coenzyme Q10 have not shown any significant benefits and thus are not recommended for the treatment of CRF during active oncological treatments.

Other integrative interventions

Mindfulness-based stress reduction (MBSR) is a multimodal programme focused on improving well-being and health. The curriculum consists of three major components: (1) experiential practice of gentle Hatha yoga (including yoga stretches, poses, and breathing and meditation exercises) performed once a week during 90-minute sessions and at home; (2) educational materials related to mindfulness, relaxation, meditation, and yoga; and (3) group processing and discussion.

Speca and colleagues demonstrated greater reductions in CRF among 109 early- or late-stage cancer patients participating in an MBSR programme, compared with participants in a waitlist control group.[26] While results of these studies are positive and suggest that MBSR may be a useful therapeutic intervention for improving CRF, the evidence is preliminary. There is a need for appropriately powered RCTs, with CRF as a primary outcome, to create an informed scientific evidence base to design clinical care.

Question 5. How is exercise prescribed?

Physical exercise is an integrative, non-pharmacologic behavioural intervention that shows great promise in mitigating CRF experienced by cancer patients during and after treatment. Exercise is defined as physical activity performed in a systematically dosed manner (i.e. frequency, intensity, duration, and mode), with the intention of improving health-related outcomes, such as depression, sleep, and fatigue, among others.[27]

Multiple systematic reviews and meta-analyses evaluating physical exercise in patients with cancer have documented improvement in CRF, physical and muscular strength, activity levels, and aerobic fitness.[28,29] Evidence shows that physical exercise of moderate intensity can attenuate systemic inflammation and improve CRF, allowing patients with or without cachexia to become more capable of performing ADLs. This improves the functional quality of life (QOL).[30] Despite the evidence for exercise in the management of CRF, an exact exercise prescription during active treatment in these patients does not exist. Most exercise prescription guidelines broadly focus on the general well-being of patients with cancer, encouraging 150 minutes/week of aerobic exercise, 2 days/week of strength training, and flexibility exercise on days when aerobic or resistance exercise is not performed.[31]

Types of physical exercise

Exercises of moderate intensity are described as those which fall between 5 and 8 metabolic equivalents (METS—procedure to quantify the energy cost of activities). These include activities that take as much effort as brisk walking (5 km/hour), stationary bike with light effort, and home-based exercises.[32] There has been a growing interest in using physical exercise as a supplementary treatment modality, with increasing research in patients at various stages of their cancer trajectory. In patients with cancer during and post-treatment, prolonged inactivity and lack of exercise may lead to loss of skeletal muscle mass and strength, which gradually affects their ability to perform simple ADLs (e.g. walking up the stairs or maintaining body balance). This 'deconditioned' state of the body leads to a myriad of ailments and symptom complex. 'Reconditioning' of this state can be achieved through a structured exercise programme designed to increase skeletal muscle mass and strength and improve QOL of these patients.[33,34] A meta-analysis of 44 studies including 3254 patients with cancer concluded that moderate-intensity resistance exercise reduced fatigue.[14] Muscle strength and better physical functioning were also shown to be significantly greater in patients undergoing moderate- to high-intensity combined resistance and aerobic exercise.[35] A 2012 Cochrane analysis included 56 randomized trials (n = 4826), 36 of which were conducted among participants undergoing active cancer treatment. Exercise resulted in a decrease in fatigue from baseline to 12 weeks' follow-up.[30] Based on current knowledge and the results of multiple randomized controlled trials and systematic reviews,[36,37] physical exercise can be recommended in non-cachectic patients with cancer.

QOL benefits resulting from increased physical activity may vary with the stage of cancer, treatment modality, and patients' current lifestyle. Improvement may be attributed to the exercise programmes, the result of increased attention by healthcare personnel, and might reflect benefits

accrued from group activities with fellow patients.[38] In future, large randomized controlled trials with a focus on study quality are required to explore the effect of physical exercise on QOL of patients with advanced cancer.

Safety in exercise

Exercise tolerance and several patient-reported outcomes can be improved with structured exercise training across a range of oncological settings. Exercise is a safe, well-tolerated intervention for patients with curative disease, both during and after adjuvant therapy. However, patients with an underlying comorbidity and receiving a range of systemic therapies may have exercise-related complications. Therefore, a history and physical examination of all the systems must be assessed.

A safe, effective exercise prescription is based on the individual and tailored to that individual's needs. Fundamental principles of exercise must be followed such as: frequency (sessions per week), intensity (how hard per session), time (session duration), and type (exercise modality). The American College of Sports Medicine (ACSM) guidelines[39] recommend that patients with cancer should participate in at least 150 minutes of moderate exercise (e.g. brisk walking, light swimming) or 75 minutes per week of vigorous exercise (e.g. jogging, running, hard swimming).

Future directions in cancer fatigue

As more physicians and other healthcare givers are introduced to the additional benefits of physical activity, exercise, and rehabilitation, more research questions will be posed, which will result in a better understanding of:

1. The importance of regular physical activity before and after a cancer diagnosis.
2. Whether length and quality of survival are prolonged equally for all modes of exercise.
3. The role that the fatigue experience plays in the psychosocial and behavioural adaptation of long-term cancer survivors' health and well-being and the measurement thereof.
4. Muscle, mental, and emotional fatigue and loss of endurance in patients undergoing different treatments for cancer.
5. The causative factors of appetite and weight loss and their role in the development of fatigue and other functional losses in patients with cancer.
6. Novel management strategies to cope with, and alleviate, fatigue.
7. The role of CIS in the aetiology of fatigue.

Case 11.1 (continued)

N.M's disease has continued to progress. She now has metastatic disease to her liver and intraperitoneal cavity. She is bothered by ascites and profound cachexia. She spends most of her day in bed. Methylphenidate no longer is helpful, and she does not wish to take it. She has no interest in getting up, but her husband wonders if there is anything else that could give her more energy at this stage. What would you tell him?

For patients and their families with advanced cancer, the following advice may be helpful:

1. Plan activities in advance for the time of day when patients feel less tired and include rest times.
2. Integrate regular gentle activities such as strolling, stretching, and sitting at a table for meals.
3. Try and avoid stress and include relaxation techniques or meditation as a daily standard.
4. Suggest multiple short naps, rather than one longer period.

5. Limit visiting hours for friends and family.
6. Consult with Meals on Wheels or other home delivery meal companies.

Case 11.2

D.R. has had chronic obstructive pulmonary disease (COPD) for several years and was functioning relatively well. However, over the last few months, he has noted more shortness of breath on exertion and moderate fatigue. He is otherwise well, with no new symptoms or illness, and has not changed or added any medications. He asks if the fatigue is part of his condition. What would you tell him?

Non-cancer fatigue

Fatigue is common in many chronic conditions and can become progressively more problematic for the patient as the illness continues and the patient comes closer to the end of their life. Clinicians need to be aware of this disabling symptom and the impact it can have on the patient's sense of well-being and ability to care for themselves. The same degree of vigilance to identify fatigue in the non-cancer patient is required as it is with cancer patients. The treatments are the same. Exercise for the patient with a moderately good performance status can be helpful. Stimulants have a potential role as well. Patients require education about fatigue and need to learn how to optimize their activities in order to cope.

Conclusion

Fatigue is a common and distressing symptom. Early assessment is important. There are many interventions that may be helpful for patients. Exercise is a key form of treatment in the early stages. Medications and good nutrition have a role to play as well. Patients and caregivers need to be educated about the cause of the fatigue and should receive appropriate therapies and be given defined goals for management.

References

1. **Anderson F**, **Downing GM**, **Hill J**, **Casorso L**, **Lerch N** (1996) Palliative performance scale (PPS): a new tool. *J Palliat Care*, **12**, 5–11.
2. **Bruera E**, **Keuhn N**, **Miller MJ** *et al.* (1991) The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care*, **7**, 6–9.
3. **Mendoza TR**, **Wang XS**, **Cleeland CS** *et al.* (1999) The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer*, **85**, 1186–96.
4. **National Comprehensive Cancer Network** (2003) Distress management. Clinical practice guidelines. *J Natl Compr Cancer Netw*, **1**, 344–74.
5. **Simmonds MJ** (2002) Physical function in patients with cancer: psychometric characteristics and clinical usefulness of a physical performance test battery. *J Pain Symptom Manage*, **24**, 404–14.
6. **Berger AM**, **Mooney K**, **Alvarez-Perez A** *et al.* (2015) Cancer-related fatigue, version 2.2015. *J Natl Compr Cancer Netw*, **13**, 1012–39.
7. **Stone P**, **Richardson A**, **Ream E** *et al.* (2000) Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. *Ann Oncol*, **11**, 971–5.
8. **Olson K**, **Turner AR**, **Courneya K**, **Field C**, **Man G**, **Cree M** (2008) Possible links between behavioural and physiological indices of tiredness, fatigue, and exhaustion in advanced cancer. *Support Care Cancer*, **16**, 241–9.

9. **Wang XS** (2008) Pathophysiology of cancer-related fatigue. *Clin J Oncol Nurs*, **12**(5 Suppl), 11–20.
10. **Mock V**, **Atkinson A**, **Barsevick AM** *et al.* (1997) Cancer-related fatigue. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw*, **5**, 1054–78.
11. **Yellen SB**, **Cella DF**, **Webster K** *et al.* (1997) Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*, **13**, 63–74.
12. **Smets EMA**, **Garssen B**, **Bonke B**, **De Haes JC** (1995) The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*, **39**, 315–25.
13. **Barsevick AM**, **Dudley W**, **Beck S**, **Sweeney C**, **Whitmer K**, **Nail L** (2004) A randomized clinical trial of energy conservation for patients with cancer-related fatigue. *Cancer*, **100,** 1302–10.
14. **Brown JC**, **Huedo-Medina TB**, **Pescatello LS** *et al.* (2011) Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, **20**, 123–33.
15. **Speck RM**, **Courneya KS**, **Masse LC** *et al.* (2010) An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv*, **4**, 87–100.
16. **Kangas M**, **Bovbjerg DH**, **Montgomery GH** (2008) Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychol Bull*, **134**, 700–41.
17. **Duijts SF**, **Faber MM**, **Oldenburg HS**, **van Beurden M**, **Aaronson NK** (2011) Effectiveness of behavioral techniques and physical exercise on psychosocial functioning and health-related quality of life in breast cancer patients and survivors—a meta-analysis. *Psychooncology*, **2**, 20.
18. **Minton O**, **Richardson A**, **Sharpe M**, **Hotopf M**, **Stone PC** (2001) Psychostimulants for the management of cancer-related fatigue: a systematic review and meta-analysis. *J Pain Symptom Manage*, **41**, 761–7.
19. **Bruera E**, **El Osta B**, **Valero V** *et al.* (2007) Donepezil for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *J Clin Oncol*, **25**, 3475–81.
20. **Roscoe JA**, **Morrow GR**, **Hickok JT** *et al.* (2005) Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. *Breast Cancer Res Treat*, **89**, 243–9.
21. **Yennurajalingam S**, **Frisbee-Hume S**, **Palmer JL** *et al.* (2013) Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *J Clin Oncol*, **31**, 3076–82.
22. **Paulsen O**, **Klepstad P**, **Rosland JH** *et al.* (2014) Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. *J Clin Oncol*, **32**, 3221–8.
23. **Barton DL**, **Liu H**, **Dakhil SR** *et al.* (2013) *Wisconsin ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. J Natl Cancer Inst*, **105**, 1230–8.
24. **Cruciani RA**, **Zhang JJ**, **Manola J**, **Cella D**, **Ansari B**, **Fisch MJ** (2012) L-carnitine supplementation for the management of fatigue in patients with cancer: an Eastern Cooperative Oncology Group phase III, randomized, double-blind, placebo-controlled trial. *J Clin Oncol*, **30**, 3864–9.
25. **Lesser GJ**, **Case D**, **Stark N** *et al.*; **Wake Forest University Community Clinical Oncology Program Research Base** (2013) A randomized, double-blind, placebo-controlled study of oral coenzyme Q10 to relieve self-reported treatment-related fatigue in newly diagnosed patients with breast cancer. *J Support Oncol*, **11**, 31–42.
26. **Speca M**, **Carlson LE**, **Goodey E**, **Angen M** (2000) A randomized, wait-list controlled clinical trial: the effect of a mindfulness meditation-based stress reduction program on mood and symptoms of stress in cancer outpatients. *Psychosom Med*, **62**, 613–22.
27. **American College of Sports Medicine**, **Whaley MH**, **Brubaker PH**, **Otto RM**, **Armstrong LE** (2006) *ACSM's Guidelines for Exercise Testing and Prescription*. Lippincott Williams & Wilkins, Philadelphia, PA.
28. **McMillan EM**, **Newhouse IJ** (2011) Exercise is an effective treatment modality for reducing cancer-related fatigue and improving physical capacity in cancer patients and survivors: a meta-analysis. *Appl Physiol Nutr Metab*, **36**, 892–903.

29. **Puetz TW**, **Herring MP** (2012) Differential effects of exercise on cancer-related fatigue during and following treatment: a meta-analysis. *Am J Prev Med*, **43**, e1–24.
30. **Mishra SI**, **Schere RW**, **Geigle PM** *et al.* (2012) Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev*, **8**, CD007566.
31. Fabi Alexandra, Bhargava Ravi, Ripamonti Carla *et al.* (2020) Cancer-related fatigue: European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis and treatment. *Annals of Oncology*, **31**(6), 13–723; doi:https://doi.org/10.1016/j.annonc.2020.02.016.
32. **Jetté M**, **Sidney K**, **Blümchen G** (1990) Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*, **13**, 555–65.
33. **Burr JF**, **Shephard RJ**, **Jones LW** (2012) Physical activity for cancer patients: clinical risk assessment for exercise clearance and prescription. *Can Fam Physician*, **58**, 970–3.
34. **Clague J**, **Bernstein L** (2012) Physical activity and cancer. *Curr Oncol Rep*, **14**, 550–8.
35. **van Waart H**, **Stuiver MM**, **van Harten WH** *et al.* (2015) Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomized clinical trial. *J Clin Oncol*, **33**, 1918–27.
36. **Oldervoll LM**, **Kaasa S**, **Hjermstad MJ**, **Lund JA**, **Loge JH** (2004) Physical exercise results in the improved subjective well-being of a few or is effective rehabilitation for all cancer patients? *Eur J Cancer*, **40**, 951–62.
37. **Courneya KS**, **McKenzie DC**, **Mackey JR** *et al.* (2013) Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. *J Natl Cancer Inst*, **105,** 1821–32.
38. **Courneya KS**, **Mackey JR**, **McKenzie DC** (2002) Exercise for breast cancer survivors: research evidence and clinical guidelines. *Phys Sportsmed*, **30**, 33–42.
39. **Schmitz KH**, **Courneya KS**, **Matthews C** *et al.* (2010) *American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc*, **42**, 1409–26.

Chapter 12

Delirium

Shirley H. Bush, Bruno Gagnon, and Peter G. Lawlor

Attitude

To enable each learner to:

- Identify that cognitive impairment is seen in both delirium and dementia.
- Explain the importance of objectively assessing cognition, given that cognitive impairment is frequently missed or misdiagnosed.
- Recognize that cognitive impairment is reversible in many episodes of delirium, and avoid adopting an unduly nihilistic approach to investigation and management.
- Recognize that cognitive impairment, as part of delirium, is a normal accompaniment of the last hours or days of life for most patients receiving palliative care.
- Reflect on the impact of delirium on patient comfort, family distress, and caregiver burden.
- Summarize the challenges involved in assessing other symptoms in the context of cognitive impairment.

Skills

To enable each learner to:

- Write a management plan for delirium in palliative care patients that includes:
  - Addressing the underlying causes.
  - Communicating with patients, families, and caregivers.
  - Non-pharmacological and pharmacological interventions.
- Demonstrate a patient- and family-centred approach to the management of delirium that recognizes the goals of care.
- Discuss issues relating to the perception and response of family members to a patient with delirium.

Knowledge

To enable each learner to:

- Describe the epidemiology of cognitive impairment and delirium at the end of life.
- List commonly used screening tools for delirium.
- Define delirium according to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) core diagnostic criteria.
- Describe the clinical presentations of delirium.
- Review the pathophysiology and pathogenesis of delirium.

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- Recognize the multifactorial aetiology of delirium.
- Differentiate delirium from dementia and depression.
- Determine the reversibility of cognitive impairment based on the assessment and recognition of precipitants that are superimposed on pre-delirious vulnerability or risk profile.

Case 12.1

Scene 1

You are called to the emergency room to assess J.W., a 70-year-old man who was diagnosed 1 year ago with non-small cell lung cancer. His cancer was advanced at diagnosis and he presented with a left-sided pleural effusion and bone metastases.

He received palliative radiation therapy to painful thoracic bone metastases 6 weeks ago. At that time, a computed tomography (CT) scan showed a liver metastasis 3 cm in diameter. His family physician prescribed citalopram 20 mg orally daily for increasing symptoms of depression. J.W. had been managing well on a regular analgesic regimen of slow-release morphine 60 mg orally every 12 hours and immediate-release morphine 10 mg orally every hour, as needed, for breakthrough pain. He has been reluctant to take his laxatives but regularly takes his oral antihypertensive medication. In addition, during a recent cancer clinic visit, he was prescribed lorazepam 1 mg sublingually every 4 hours, as needed, for anxiety.

Two weeks ago, J.W. started to experience pain in his left hip. He has found it more painful when walking, and despite taking six extra doses of immediate-release morphine for the last couple of days, he has experienced little relief. He has become sleepy during the day and complains of nausea. Consequently, he has had little solid or liquid intake over the last 2 days. His wife has found him to be vague and confused at times, and she has witnessed episodes of jerking of his legs. He complains of seeing shadows of people in the curtains. As he appeared to be anxious, his wife has given him a total of four doses of lorazepam in the last 24 hours. However, he continues to have poor sleep. At night, he is restless and disoriented, keeps calling out and trying to get out of bed, and has been incontinent of urine on two occasions. His wife and family are fearful that he is either 'losing his mind or going senile' or 'deeply depressed'. They are worried that he is close to death. His youngest son has just taken a 7-hour flight to be with him. His son is angry about the level of care, as he perceives the major problem to be one of poor pain control.

Question 1. How common is cognitive impairment in patients like J.W. with advanced cancer?

Cognitive impairment can present mainly as part of either a delirium or dementia, or as part of a delirium superimposed on dementia. Dementia is the development of memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning.[1] Dementia is usually insidious in onset, with slowly progressing changes over years, as opposed to the acute onset and fluctuating nature of delirium from day to day. Dementia is a risk factor for delirium, and when a delirium is superimposed on dementia, it portends a poorer course and prognosis.[2] Occasionally, mild cognitive dysfunction can occur as part of depression (depressive pseudodementia). Other psychotic disorders might also be considered, but they are commonly associated with a prior history of similar episodes. The diagnosis of delirium superimposed on dementia is often only made when some of the features of delirium subside with treatment of underlying precipitating causes, subsequently revealing an underlying

dementia. Persistent delirium in older hospitalized patients occurs frequently and is associated with deterioration in cognition and functional decline.[3]

Cognitive impairment has been documented in 42–44% of patients on admission to palliative care units.[4] Delirium, which is the most common neuropsychiatric complication of cancer, has been detected in 40% of advanced cancer patients on admission to a palliative care unit.[5] Almost 90% of patients with advanced cancer develop delirium in the final hours to days before death.[6,7]

This chapter will focus predominantly on cognitive impairment as part of an acute delirium.

Question 2. What are the core criteria for a diagnosis of delirium? What are the additional associated clinical features?

The DSM-5 lists the major criteria for making a diagnosis of delirium due to a general medical condition.[8]

Criterion A requires a disturbance in attention and awareness. Criterion B describes the time course with delirium usually having an acute onset and a tendency to fluctuate over the day. There should be also an additional disturbance in cognition (criterion C). Finally, there should be evidence (from the history or clinically) for one or more precipitants: an organic aetiology, an exogenous substance (e.g. a psychoactive drug such as a tricyclic antidepressant), substance withdrawal (e.g. alcohol withdrawal), or toxin.

Other associated clinical features of delirium that are not formally part of the DSM-5 criteria include disturbance of the sleep–wake cycle, delusional thinking, emotional lability, and altered psychomotor activity. Clinical subtypes of delirium are classified according to the type of alteration in psychomotor activity, namely hyperactive (or agitated), hypoactive, or a mixed form with both hyper- and hypoactive features. In palliative care patients, the majority of delirium episodes are of the hypoactive or mixed subtype, and are usually multifactorial in origin, with a median of three (range 1–6) precipitants per delirium episode.[5] Although the clinical features of common underlying causes should be sought and identified, the presence of delirium may sometimes be the sole clinical manifestation of a major life-threatening condition such as sepsis.

A prodromal period, often with single symptoms of mild intensity such as disorientation, anxiety, restlessness, irritability, and particularly sleep–wake cycle disturbance, may sometimes precede the onset of florid delirium by a few days.[8,9]

Question 3. Why might delirium be either missed or misdiagnosed? For J.W., what are the consequences of missing the diagnosis or misdiagnosing the syndrome?

Misdiagnosis or failure to recognize delirium is common.[10,11] The ambiguous terms that are used to describe symptoms of delirium—such as pseudosenility, confusional state, or terminal restlessness—can contribute to the lack of diagnostic clarity and possibly discourage further investigation. Other reasons cited for its under-recognition include failure to regularly screen for delirium, fluctuation in the intensity of delirious symptoms (e.g. the occurrence of a lucid interval), and the presence of the hypoactive subtype. The hypoactive delirious patient is often quiet and withdrawn—and therefore behaves as a 'good' patient—in contrast to the agitated hyperactive patient whose behaviour is more likely to attract attention, and possibly thereby results in recognition of delirium and prompts its treatment in a timely fashion. Delirium superimposed on dementia is arguably more difficult to diagnose.

Delirium most commonly tends to be misdiagnosed as depression or dementia. Cognitive impairment, perceptual disturbances, and psychomotor abnormalities occur in both dementia and delirium. However, in dementia, there is little or no clouding of consciousness. In the case of hypoactive or emotionally labile patients, depression is often diagnosed in error. Hyperactive delirium may be misdiagnosed as a manic or psychotic episode, anxiety, or akathisia.

Failure to diagnose J.W.'s delirium could be associated with an increase in morbidity or even death, especially if potentially reversible underlying causes of delirium have not been sought and identified. Delirium has been reported to be reversible in approximately 50% of episodes in patients with advanced cancer.[5] Wrongly diagnosing J.W.'s delirium as depression or anxiety and commencing an antidepressant or a benzodiazepine could lead to worsening of his delirium. Disinhibition and increased pain expression in an agitated delirious patient may be misinterpreted as a worsening pain syndrome, with resulting increased opioid administration exacerbating the delirium.

Question 4. How might the history and physical assessment help to clarify the diagnosis?

A collateral history from J.W.'s wife would be essential to establish the fluctuating nature of his mental status and the temporal onset of his cognitive decline. Dementia is characterized by an insidious onset over months to years, whereas delirium usually develops over hours to days. Fluctuation in the clinical presentation of symptoms, especially awareness, is much more likely to occur in delirium than in dementia. However, symptoms may fluctuate in some dementias, especially dementia with Lewy bodies (DLB) with core clinical features of fluctuating cognition, recurrent complex visual hallucinations, and parkinsonism. Your interaction with J.W., together with a formal cognitive assessment, should identify the attentional deficit, which is so typically characteristic of delirium, as opposed to dementia. Delusions in patients with delirium tend to be loosely held (i.e. are not always present), whereas psychoses, such as schizophrenia, are characterized by more consistently held delusions. One might ask about the presence of opioid-induced neurotoxicity (OIN) features such as 'jerky movements' or myoclonus, tactile or visual hallucinations, severe sedation, hyperalgesia (increased response to painful stimulus), or allodynia (pain associated with a non-painful stimulus like light touch).[12]

Physical examination should be comprehensive in an effort to identify underlying causes of delirium such as dehydration, infection, and neurological signs such as cranial nerve deficits associated with leptomeningeal disease. Abnormal movements, such as asterixis (e.g. with hepatic encephalopathy) and myoclonus, should be identified.

Question 5. What tools are most appropriate for use in the initial and ongoing assessment of J.W.'s cognitive status?

A large number of instruments have been developed to assess delirium, each with different strengths and limitations with regard to use within the palliative care setting.[13,14] Some of these instruments involve a large component of active patient participation and therefore are unduly burdensome in patients such as J.W. It should be noted that the Mini-Mental State Examination (MMSE)[15] and the Short Orientation Memory Concentration Test (SOMCT) or Blessed Orientation Memory Concentration (BOMC) test[16] are used to assess cognitive function and detect deficits as part of a delirium, dementia, or both. The SOMCT or BOMC assesses attentional capacity, which is characteristically impaired in delirium, through the counting of 20 to 1 backwards and reciting the months of the year backwards. At the bedside, the Months of the Year Backward (MOTYB) test is

a simple tool which has been used to quickly measure attention,[17] and other tools to assess visual attention have been developed.[18]

The Confusion Assessment Method (CAM) is a well-validated, yet suitably brief, instrument that has been widely used in the screening and diagnosis of delirium.[19] The CAM is rated on the basis of clinician interaction with the patient and assesses the presence or absence of four criteria: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. The CAM algorithm for diagnosis of delirium requires the presence of both the first and the second criteria, and either the third or the fourth criterion. The CAM is a copyrighted instrument which requires training in its use, and both the CAM tool and the associated training manual are available online.[20] The CAM has been validated in the palliative care setting.[21] Tools such as the Nursing Delirium Screening Scale (Nu-DESC)[22] and the Delirium Observation Screening (DOS) scale[23] are entirely observational and nurse-rated. The 10-item Memorial Delirium Assessment Scale (MDAS)[24] (clinician-rated and partly observational) and the 16-item clinician-rated Delirium Rating Scale-Revised-98 (DRS-R98)[25] capture the behavioural changes of delirium and can be used to monitor the severity of delirium.

Case 12.1 (continued)

A collateral history from J.W.'s wife suggests that the cognitive deficit and behavioural disturbance began less than 1 week ago. They have fluctuated over the course of the day, with periods of relative lucidity on some mornings. J.W. has no past history of any psychiatric disorder. He was able to give a history of tactile, as well as visual hallucinations. Cognitive assessment using the SOMCT suggested mild cognitive impairment. His CAM assessment was positive for the first three criteria, and you therefore make a diagnosis of delirium. The relevant positive findings on physical examination are signs of dehydration, moderate cachexia, multifocal myoclonus of his limbs, and mild pedal oedema. He is mildly agitated and intermittently tearful.

Question 6. What are the major aetiological factors associated with delirium in the palliative care setting? What are J.W.'s risk factors and what are the possible precipitants of his delirium?

The aetiology of delirium is generally multifactorial, invariably involving organic factors. Organic factors have been classified as primary cerebral disease, systemic disease affecting the brain secondarily, exogenous toxic agents such as opioids and other psychoactive medications or substances of abuse, and withdrawal syndromes (e.g. from alcohol or benzodiazepines).[26] These organic factors are outlined in Table 12.1. Environmental factors, such as movement out of a familiar home setting, can contribute to the symptoms from underlying organic processes.

In addition to the predisposing risk factors that commonly occur in non-cancer patients (such as advanced age, pre-existing cognitive impairment, and reduced sensory input due to poor vision or deafness), the underlying vulnerability towards the development of delirium in patients with advanced cancer is increased. This is due to likely predisposing factors such as hypoalbuminaemia,[27] cachexia, pro-inflammatory cytokines,[28] and paraneoplastic neural autoantibodies.[29]

Urinary retention and constipation are factors that can aggravate agitation, especially in the elderly. Various precipitants, such as medications or infection, are superimposed on this high level of underlying vulnerability, culminating in an episode of delirium.

Table 12.1 Aetiological factors associated with delirium in advanced cancer

Category	Cause
Medications	
Psychoactive	Opioids; benzodiazepines; tricyclic antidepressants; anticonvulsants; anticholinergics; selective serotonin reuptake inhibitors; antipsychotics
Others	Corticosteroids; histamine H2 blockers; omeprazole; ciprofloxacin; aciclovir
Withdrawal reaction	Alcohol; psychoactive medications such as benzodiazepines; nicotine
Intracranial disease	Primary and metastatic brain tumour; leptomeningeal disease; post-seizure; non-convulsive status epilepticus; CVA
Systemic disease	
Organ failure	Cardiac; hepatic; renal; respiratory
Infection	Any site, but especially pulmonary and urinary; sepsis
Haematological	Anaemia; disseminated intravascular coagulation
Metabolic	Dehydration; hypercalcaemia; hyponatraemia; hypernatraemia; hypomagnesaemia; hypoglycaemia
Endocrine	Hypothyroidism; hypoadrenalism
Nutritional deficiency	Thiamine (vitamin B_1); folic acid (vitamin B_9); cobalamin (vitamin B_{12})
Paraneoplastic	For example, encephalitis

CVA, cerebrovascular accident.

Source: data from Bush SH, Lawlor PG, Ryan K, et al (2018). 'Delirium in adult cancer patients: ESMO (European Society for Medical Oncology) Clinical Practice Guidelines'. Ann Oncol, Vol. 29, Supplement_4, pp, iv143–65.

In the case of J.W., potential risk factors to consider include his age, nutritional status, hepatic impairment (this might not be due to the single liver metastasis but could be due to hitherto undiagnosed pre-existing liver disease), anaemia, and possible undiagnosed brain metastases or leptomeningeal disease. In addition, precipitants such as medications (morphine, lorazepam, and citalopram), electrolyte disturbance (e.g. hypercalcaemia or hyponatraemia), hypoxia, dehydration, and underlying infection need to be considered.

Question 7. What is the pathogenesis of delirium?

Delirium is considered to be a global disorder of brain function. The neurotransmitter hypothesis explained the occurrence of delirium due to a reduction in cholinergic transmission or at least an altered balance with a relatively greater reduction of cholinergic transmission, with respect to dopaminergic transmission.[30] However, it is now known that the pathophysiology of delirium is much more complex. Maldonado has detailed additional hypotheses: neuronal ageing, neuroinflammatory, oxidative stress, neuroendocrine, and circadian rhythm dysregulation.[31] Many other neurotransmitters, such as cortisol, gamma-aminobutyric acid (GABA), serotonin, glutamate, norepinephrine, and melatonin, have been implicated in the pathogenesis of

delirium.[11,32] Pro-inflammatory cytokines in the setting of J.W.'s advanced disease are also considered to have a role in this complex process.

Medications, including opioids, are a common contributory precipitating factor for delirium (see Table 12.1). Morphine is metabolized mainly to morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). The M6G metabolite is active at the μ-opioid receptor and contributes to analgesia. However, the M3G metabolite does not bind to opioid receptors. It has been shown to be neuroexcitatory in animal studies, and it is postulated that it may contribute to the OIN features (e.g. myoclonus, delirium, and allodynia) associated with morphine. Hydromorphone-3-glucuronide, a metabolite of hydromorphone, has also shown to be neuroexcitatory in animal studies. Other mechanisms for OIN have been suggested, including activation of N-methyl-D-aspartate receptors and a non-opioid receptor-mediated mechanism.[33,34] However, the precise pathophysiological mechanisms underlying OIN have yet to be elucidated. In addition to escalating doses of opioid, other factors predisposing to OIN include dehydration, renal failure, and infection.[12] Many medications (e.g. tricyclic antidepressants such as amitriptyline) have anticholinergic side-effects. Reduced cerebral cholinergic transmission in dementia is proposed as the explanation for the greater risk of delirium in these patients.[35]

Question 8. What impact does the diagnosis of delirium have on J.W., his family, and you and other healthcare professionals?

The wide spectrum of thought and behavioural disturbance involving hallucinations and delusions, with a background of disorientation, is almost certainly a highly distressing experience for J.W. His intermittent urinary incontinence is also related to his delirium. Despite many attempts to climb out of bed, he has not sustained any falls or injuries. The presence of delirium has rendered him mentally incompetent in relation to conducting his financial affairs and participating in the therapeutic decision-making process. For both J.W. and his family, delirium is impeding meaningful communication at a critical time. This is particularly distressing for his son who has made a long journey to be with his father and finds that he now cannot discuss many issues with him in the way that he used to do. The perception of his father in unrelieved pain and the son's consequent anger could potentially complicate the bereavement process. Furthermore, the memory of this image could have a negative impact on all those present, when they encounter a terminal illness at a later date.

For the nursing staff and the other members of the healthcare team, the presence of delirium creates great difficulty in assessing pain and other symptoms. Delirious patients have been noted to receive a higher number of breakthrough doses of opioid analgesics in the evening and at night, whereas non-delirious patients use more doses in the daytime.[36] This suggests that either restlessness associated with 'sundowning' could give rise to more movement-associated pain or the agitation could be misinterpreted as being pain-related. In this situation, conflict commonly arises between the patient, their family, and the staff concerning the level of analgesia and the need for opioid dose escalation. A common scenario that can emerge is when the patient's distress causes marked emotional distress in family caregivers who advocate an increase in opioid dose to reduce the patient's distress (and, indirectly, their own distress).[37] Unfortunately, this could further exacerbate the agitation if the opioid is already contributing to the delirium. It is also possible that J.W.'s son may vent some anger towards the healthcare team. The provision of education and ongoing psychosocial support to the family is essential, as delirium is known to cause significant distress to patients and their families.[38]

Case 12.1 (continued)

In his advance directive, J.W. has named his only daughter F.W. as his substitute decision-maker. His son is feeling guilty about living so far away from home. In addition, he indicates that he is tired after his long journey, despondent about the extent of his father's deterioration since he last saw him 6 months ago and angry at what he perceives to be his father's uncontrolled pain. He proceeds to advocate strongly for his father, and he expresses his concerns in an abusive way towards the nursing staff.

Question 9. What is your initial approach to management of a potentially reversible delirium?

An algorithm for a general approach to management of delirium might involve the following steps:

- Identify the underlying causes and assess if it is possible and appropriate to treat and reverse them. It is less appropriate to aggressively investigate delirium in a patient who is in the last hours of life and actively dying.
- Assess the potential burden associated with correcting any underlying causes of delirium, and the consequent impact on quality of life (e.g. establishing an intravenous line for bisphosphonate administration).
- Meet with the patient (who may be capable of some input if there are fluctuations in the severity of their delirium) and the patient's family in order to facilitate informed decision-making and a consensus on the goals of care.
- Treat the symptoms of delirium (which is *always* an appropriate approach):
  - Non-pharmacologically with environmental measures and other measures (see Question 12 below). Explain to the family, the patient (if possible), and other caregivers what is happening and what the treatment strategy is. Education about the nature of delirium and the usually poor prognosis when it occurs with advanced illness at the end of life is important.
  - Pharmacological intervention may be required if the patient is extremely agitated causing safety concerns or is experiencing distressing perceptual disturbances such as vivid hallucinations.[14]
- Provide information and emotional support for the patient and family.

Question 10. How would you apply this management strategy in J.W.'s case? In particular, how would you approach J.W.'s verbally abusive son?

Following your initial history and physical examination, you meet with J.W.'s family to discuss your preliminary findings and the goals of care. You explain the nature of delirium, particularly the seriousness of this diagnosis, but also the potential for reversal in up to 50% of episodes, depending on the cause. You explain that although pain should be treated, the presence of emotional lability and agitation is also probably associated with the delirium. J.W.'s son is able to express his feelings in this meeting, including his guilt. Further meetings are arranged for him to have some counselling from the team social worker. J.W.'s son now appears to have acquired a better understanding of his father's presentation and is grateful for your informative efforts. He personally acknowledges that some of his anger was projected towards the nursing staff and is extremely apologetic about this.

The consensus reached at the family meeting was that reversible precipitants of J.W.'s delirium should be sought and treated, and the goal of treatment was to optimize his quality of life and comfort. The family was assured that they would be regularly updated of J.W.'s status. The importance of team communication on the medical unit was emphasized, so that J.W. and his family received consistent and non-conflicting responses to their questions from staff members. J.W.'s advance directive refers to his desire not to have aggressive resuscitation measures such as cardiopulmonary resuscitation, intubation, and defibrillation. This was clearly documented on his hospital chart.

The reversibility of delirium in this situation is likely to depend on the identification of reversible precipitants such as psychoactive medications, dehydration, hypercalcaemia, anaemia, and infection. Underlying factors associated with progressive disease such as cachexia, hepatic impairment, and hypoalbuminaemia are less amenable to treatment. The approach to opioid neurotoxicity is either to reduce the dose or to switch to a different opioid and hydrate the patient (normally using a subcutaneous infusion known as *hypodermoclysis*, as this can be easier to start and maintain than an intravenous line), in addition to symptomatic management (see Question 12 below).

Constipation frequently accompanies delirium. It is unclear whether constipation is a contributory cause of delirium or whether, as is perhaps more likely, it occurs in association with delirium and its underlying causes (e.g. opioid treatment, dehydration, and hypercalcaemia).

Question 11. What laboratory and radiological investigations might you recommend for J.W.?

Preliminary laboratory tests aimed at identifying some reversible causes might include a complete blood count, electrolytes, urea, creatinine, calcium, albumin, magnesium, random blood glucose, bilirubin, liver enzymes, ammonia levels (if severe liver impairment is suspected), urinalysis, or urine culture. Moderate elevation of J.W.'s urea levels would support your clinical impression of dehydration.

Rarely, vitamin deficiencies such as vitamin B_{12} (cobalamin), vitamin B_6 (pyridoxine), or vitamin B_1 (thiamine) deficiency may be implicated and their treatment could lead to an improvement in cognitive function. Radiological investigation might include a chest X-ray, and a plain abdominal film to assess for constipation. Cerebral imaging with contrast enhancement is indicated if there are focal neurological signs or if the preliminary battery of laboratory tests fails to identify a precipitating cause for delirium.

Question 12. Apart from treating the underlying causes, what other options are available for symptomatic management?

Non-pharmacological interventions are an important component of delirium care in older people.[39] These include frequent orientation of the patient, using simple, clear, and concise communication, encouraging the family to assist with reorientation, strategic placement of a clock and calendar, optimal lighting, and noise reduction, and limiting staff changes or having the same nurse take care of the patient on successive days. Patients should be ambulated whenever possible, or else transferred from bed to chair or wheelchair during the day as tolerated. Most palliative care institutions will try to avoid the use of physical restraints. Robust research on the effectiveness of non-pharmacological multicomponent interventions in palliative care patients is

needed.[14] Historically, antipsychotics have been used for the symptomatic treatment of delirium. However, recent research evidence not only challenges this practice but also suggests that antipsychotics may be harmful to patients.[40,41] Known adverse effects of antipsychotics include: anticholinergic; sedative; hypotensive; extra-pyramidal side-effects (EPSEs); seizures (due to lowering of the seizure threshold); corrected QT (QTc) interval prolongation; and rarely, neuroleptic malignant syndrome.[42]

In the seminal multisite, double-blind, parallel-arm, dose-titrated randomized controlled trial in 247 adult palliative care patients by Agar *et al.*, participants were randomized to receive age-adjusted doses of oral risperidone or haloperidol or placebo over a 72-hour period.[40] Participants could receive subcutaneous midazolam every 2 hours as needed. At baseline, the participants' baseline Australia-modified Karnofsky Performance Status ranged from 30 to 50% [which roughly equates to a Palliative Performance Scale (PPS)[43] of 30–50%] and they had delirium of mild to moderate severity, as assessed by the MDAS.[24] Participants in the risperidone and haloperidol arms had higher delirium symptom severity scores and received more as-needed midazolam, as compared with those in the placebo arm. The median survival was 26 days in the placebo arm, and 17 days and 16 days for risperidone and haloperidol, respectively. Robust research examining the role of antipsychotics in palliative care populations for the management of severe delirium is warranted to provide the evidence that is required to underpin the practice of clinicians at the bedside.

Subcutaneous methotrimeprazine, a sedating phenothiazine, has often been used in the management of refractory agitated delirium at the end of life. However, due to the current lack of published research evidence to support this practice, well-designed studies evaluating methotrimeprazine are needed.[14] Benzodiazepines, such as lorazepam, should be avoided as single agents in the management of delirium in cancer patients, as they are considered to be deliriogenic,[44] but they are the drugs of choice specifically for delirium related to benzodiazepine or alcohol withdrawal.

Current delirium guideline recommendations are to only use pharmacological interventions in the lowest effective dose if patients have distressing delirium symptoms (e.g. disturbing hallucinations) or if there are safety concerns due to severe patient agitation.[14,45] Doses of antipsychotics and benzodiazepines should be reduced in older or frail patients. Medications should initially be prescribed on a PRN 'as needed' basis, although patients with persisting distressing symptoms may require scheduled dosing. Haloperidol should not be used in patients with Parkinson's disease or DLB due to the risk of EPSEs.

Case 12.1 (continued)

J.W. was found to have hypercalcaemia, opioid toxicity, and dehydration. He was admitted and his citalopram and lorazepam were discontinued. He received hydration with normal saline via hypodermoclysis, followed by an infusion of intravenous pamidronate (a bisphosphonate), and his opioid was switched to a 30% lower equi-analgesic dose of hydromorphone, with the addition of rescue doses. You prescribe haloperidol 0.5 mg subcutaneously every hour as needed for severe agitation. A chest X-ray revealed progression of metastatic lung nodules and now bilateral pleural effusions. However, his oxygen saturations remained at 94% on room air. His constipation was managed with enemas and an increase of his regular laxatives.

Within 48 hours, his agitation and perceptual disturbance had subsided and he became more oriented. By the fourth day of admission, he was CAM-negative. His family was most appreciative of the supportive care that they and J.W. had received. He was discharged home after 1 week, and his expressed wish was to remain at home with his wife for as long as possible. You have contacted his community nurse and family physician to discuss discharge plans, and in particular to regularly monitor his calcium levels. In addition, you write a discharge letter and send a copy to J.W.'s radiation oncologist, who is due to review him in 4 weeks' time.

In your discharge letter, you surmise that J.W. developed delirium due to hypercalcaemia, medications (lorazepam and citalopram), and morphine opioid-induced neurotoxicity. The latter was exacerbated by dehydration, as he was drinking less fluid, partly due to somnolence and partly because of nausea due to the hypercalcaemia and associated constipation. This episode of delirium has highlighted for you the reversibility and multifactorial aetiology of delirium, in addition to the importance of addressing family concerns.

Case 12.1 (continued)

Scene 2

J.W. has been back in his home for 3 months now. He truly enjoyed his first 8 weeks at home. He was initially mobile with the help of a walker and enjoyed sitting in his garden, which was his pride and joy. He spent some precious time with his son, who spent an additional 2 weeks with his parents before flying back home. J.W.'s daughter F.W. was granted compassionate leave from work and moved back home to help her mother to care for her father. During this time, J.W. discussed his future care wishes with his family. He told them that he did not want any more investigations or life-prolonging treatments but wished to focus on being kept comfortable and pain-free. His community nurse and family physician visited him regularly.

Over the last month, J.W. experienced physical decline, with further weight loss, fatigue, and increased difficulty taking his oral medications. He also became mildly jaundiced, was spending more time in bed, and by the end of the third month since his hospital discharge, he was completely bed-bound. He developed increasing agitation and distressing visual hallucinations, especially at night. On a home visit 2 days ago, his family physician prescribed haloperidol 1 mg subcutaneously every hour as needed for agitation.

A follow-up home visit was made by J.W.'s family physician this morning. J.W.'s daughter reported that he had been agitated for most of the previous night despite four doses of haloperidol. At one stage, he appeared to be talking to his dead mother, and at another, he was convinced that his daughter was trying to poison him. Both J.W.'s daughter and his wife are completely exhausted. F.W. spoke earlier to her brother on the phone who said that he planned to get a flight as early as possible in order to see his father. Collectively, the family feels that J.W. has 'gone through enough' and they request that no further blood tests be done, consistent with his previously stated wishes. The family physician, who is concerned about suboptimal symptom control and the family's exhaustion, raises the possibility of admission to the local hospice.

You are the palliative care consultant on call and receive a telephone call from J.W.'s family physician. He outlines the medical history for you and his concern about the physical and psychological health of the family caregivers. He is requesting hospice admission and informs you that J.W.'s substitute decision-maker is requesting that no blood tests be done. He also seeks advice in the interim about what can be done for his patient's agitation.

Question 13. How would you respond to the family physician with regard to J.W.'s status? How would your response differ if there was no advance directive in place? What would you suggest with regard to the agitation?

At this point, it is clear that J.W. is in another delirium. It is of paramount importance to respect the expressed wish of the patient (through his daughter as proxy) not to have any further blood tests. You agree to accept J.W. for admission to the hospice.

If J.W. had not drawn up an advance directive, given the major progression in his disease, the associated dramatic decrease in his functional status, and the likelihood of delirium being less reversible on the second or subsequent episodes,[5] it seems reasonable to conclude that the management of his delirium and the goals of care should be largely restricted to symptomatic treatment. Searching for underlying precipitants would be inappropriate in the context of his imminently pre-terminal status. However, often such decisions are difficult to make and need to be individualized for each patient and each episode of delirium.

You suggest a more sedating antipsychotic and request that the community nurse gives methotrimeprazine 6.25 mg subcutaneously before moving J.W. to the hospice.

Case 12.1 (continued)

J.W. is admitted to the hospice. After he has received two doses of methotrimeprazine, his agitation subsides somewhat. You meet with his wife and daughter who are relieved to see some reduction in his agitation. You decide to increase his methotrimeprazine to 12.5 mg subcutaneously every 8 hours around the clock and hourly as needed for control of agitation. Overnight, he remained agitated despite catheterization by the hospice nurse to alleviate urinary retention. It was necessary to further increase his methotrimeprazine dose to 25 mg using the same dosing schedule as previously prescribed. His agitation initially settles, but you are concerned that this may only be temporary. By the following morning, he is again intermittently agitated, and his family, who have maintained an overnight vigil by his bedside, are very distraught as a result. You meet with the family, including his son who has now arrived, and discuss the role of palliative sedation in the management of refractory agitated delirium at the end of life (see also Chapter 20 on palliative sedation). The family is in agreement that this would be in keeping with J.W's previously stated wishes. He is commenced on a continuous midazolam infusion, and the dose is titrated to alleviate his agitation. J.W. dies peacefully about 36 hours later, with his family by his bedside.

Future trends and research objectives

The projected change in society, with a burgeoning increase in the number of older people, warrants a greater awareness and understanding of the spectrum of cognitive dysfunction in palliative care. Further educational efforts are therefore necessary to improve the recognition of these disorders and their consequences. Aside from antipsychotics and benzodiazepines, there is currently limited evidence for other pharmacological interventions (such as melatonin, methylphenidate, modafinil, valproic acid, gabapentin, and ondansetron) in the management of delirium.[42] Dexmedetomidine, a highly selective α2-adrenergic receptor agonist, is used in critically ill adult patients when agitation due to delirium is impeding the weaning of mechanical ventilation or extubation. The successful use of continuous dexmedetomidine infusions in patients with cancer pain and intractable delirium has been reported in case reports, but more evidence is needed to guide clinical practice.

For delirium in palliative care patients, future research[46] should focus on:

- Phenomenological studies to better characterize the syndrome in more detail.
- The development of low-burden assessment tools.
- Predictive models of delirium reversibility.
- Prospective randomized controlled trials of non-pharmacological multicomponent interventions, with economic evaluations.

- Prospective placebo-controlled, randomized controlled trials for both the pharmacological prevention and treatment of delirium.
- Implementation studies of evidence-based guidelines.

References

1. **American Psychiatric Association** (2013) Major and mild neurocognitive disorders. In: **American Psychiatric Association**. *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn, pp. 602–43. American Psychiatric Association, Arlington, VA.
2. **Witlox J**, **Eurelings LSM**, **de Jonghe JFM**, **Kalisvaart KJ**, **Eikelenboom P**, **van Gool WA** (2010) Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*, **304**(4), 443–51.
3. **Fong TG**, **Vasunilashorn SM**, **Libermann T**, **Marcantonio ER**, **Inouye SK** (2019) Delirium and Alzheimer's disease: a proposed model for shared pathophysiology. *Int J Geriatr Psychiatry*, **34**(6), 781–89. doi: 10.1002/gps.5088
4. **Hjermstad MJ**, **Loge JH**, **Kaasa S** (2004) Methods for assessment of cognitive failure and delirium in palliative care patients: implications for practice and research. *Palliat Med*, **18**(6), 494–506.
5. **Lawlor PG**, **Gagnon B**, **Mancini IL** *et al.* (2000) Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med*, **160**(6), 786–94.
6. **Hosie A**, **Davidson PM**, **Agar M**, **Sanderson CR**, **Phillips J** (2013) Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. *Palliat Med*, **27**(6), 486–98.
7. **Massie MJ**, **Holland J**, **Glass E** (1983) Delirium in terminally ill cancer patients. *Am J of Psychiatry*, **140**(8), 1048–50.
8. **American Psychiatric Association** (2013) Delirium due to a general medical condition. In: **American Psychiatric Association**. *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn, pp. 596–602. American Psychiatric Association, Arlington, VA.
9. **Kerr CW**, **Donnelly JP**, **Wright ST** *et al.* (2013) Progression of delirium in advanced illness: a multivariate model of caregiver and clinician perspectives. *J Palliat Med*, **16**(7), 768–73.
10. **Breitbart W**, **Chochinov HM**, **Passik SD** (2010) Psychiatric symptoms in palliative medicine. In: Hanks G, Cherny N, Christakis N, Fallon M, Kaasa S, Portenoy R (eds.) *Oxford Textbook of Palliative Medicine*, 4th edn, pp. 1453–1482. Oxford University Press, Oxford.
11. **Inouye SK** (2006) Delirium in older persons. *N Engl J Med*, **354**(11), 1157–65.
12. **Bush SH**, **Bruera E** (2009) The assessment and management of delirium in cancer patients. *Oncologist*, **14**(10), 1039–49.
13. **Leonard MM**, **Nekolaichuk C**, **Meagher DJ** *et al.* (2014) Practical assessment of delirium in palliative care. *J Pain Symptom Manage*, **48**(2), 176–90.
14. **Bush SH**, **Lawlor PG**, **Ryan K** *et al.* (2018) Delirium in adult cancer patients: ESMO (European Society for Medical Oncology) Clinical Practice Guidelines. *Ann Oncol*, **29**(Supplement_4), iv143–65.
15. **Folstein MF**, **Folstein SE**, **McHugh PR** (1975) 'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*, **12**(3), 189–98.
16. **Katzman R**, **Brown T**, **Fuld P**, **Peck A**, **Schechter R**, **Schimmel H** (1983) Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. *Am J Psychiatry*, **140**(6), 734–9.
17. **Meagher J**, **Leonard M**, **Donoghue L** *et al.* (2015) Months Backward Test: a review of its use in clinical studies. *World J Psychiatry*, **5**(3), 305–14.
18. **Tieges Z**, **Evans JJ**, **Neufeld KJ**, **Maclullich AMJ** (2018) The neuropsychology of delirium: advancing the science of delirium assessment. *Int J Geriatr Psychiatry*, **33**(11), 1501–11.

19. **Inouye SK**, **van Dyck C**, **Alessi C**, **Balkin S**, **Siegal A**, **Horwitz RI** (1990) Clarifying confusion: the Confusion Assessment Method. A new method for detection of delirium. *Ann Intern Med*, **113**(12), 941–8.
20. **The Hospital Elder Life Program (HELP) for Prevention of Delirium**. Delirium Instruments, Confusion Assessment Method (CAM). https://help.agscocare.org/
21. **Ryan K**, **Leonard M**, **Guerin S**, **Donnelly S**, **Conroy M**, **Meagher D** (2009) Validation of the Confusion Assessment Method in the palliative care setting. *Palliat Med*, **23**(1), 40–5.
22. **Gaudreau J-D**, **Gagnon P**, **Harel F**, **Tremblay A**, **Roy M-A** (2005) Fast, systematic, and continuous delirium assessment in hospitalized patients: the Nursing Delirium Screening scale. *J Pain Symptom Manage*, **29**(4), 368–75.
23. **Detroyer E**, **Clement PM**, **Baeten N** *et al.* (2014) Detection of delirium in palliative care unit patients: a prospective descriptive study of the Delirium Observation Screening Scale administered by bedside nurses. *Palliat Med*, **28**(1), 79–86.
24. **Breitbart W**, **Rosenfeld B**, **Roth A**, **Smith MJ**, **Cohen K**, **Passik S** (1997) The Memorial Delirium Assessment Scale. *J Pain Symptom Manage*, **13**(3), 128–37.
25. **Trzepacz PT**, **Mittal D**, **Torres R**, **Kanary K**, **Norton J**, **Jimerson N** (2001) Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *J Neuropsychiatry Clin Neurosci*, **13**(2), 229–42.
26. **Lipowski Z** (1990) Etiology. In: Lipowski Z (ed.) *Delirium: Acute Confusional States*, pp. 109–40. Oxford University Press, New York, NY.
27. **Ljubisavljevic V**, **Kelly B** (2003) Risk factors for development of delirium among oncology patients. *Gen Hosp Psychiatry*, **25**(5), 345–52.
28. **Gupta SC**, **Kim JH**, **Kannappan R**, **Reuter S**, **Dougherty PM**, **Aggarwal BB** (2011) Role of nuclear factor-κB-mediated inflammatory pathways in cancer-related symptoms and their regulation by nutritional agents. *Exp Biol Med (Maywood)*, **236**(6), 658–71.
29. **McKeon A**, **Pittock S** (2011) Paraneoplastic encephalomyelopathies: pathology and mechanisms. *Acta Neuropathol*, **122**(4), 381–400.
30. **Trzepacz PT** (2000) Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. *Semin Clin Neuropsychiatry*, **5**(2), 132–48.
31. **Maldonado JR** (2018) Delirium pathophysiology: an updated hypothesis of the etiology of acute brain failure. *Int J Geriatr Psychiatry*, **33**(11), 1428–57.
32. **Agar M**, **Lawlor P** (2008) Delirium in cancer patients: a focus on treatment-induced psychopathology. *Curr Opin Oncol*, **20**(4), 360–6.
33. **Vella-Brincat J**, **Macleod AD** (2007) Adverse effects of opioids on the central nervous systems of palliative care patients. *J Pain Palliat Care Pharmacother*, **21**(1), 15–25.
34. **Mercadante S**, **Ferrera P**, **Villari P**, **Arcuri E** (2003) Hyperalgesia: an emerging iatrogenic syndrome. *J Pain Symptom Manage*, **26**(2), 769–75.
35. **van Gool WA**, **van de Beek D**, **Eikelenboom P** (2010) Systemic infection and delirium: when cytokines and acetylcholine collide. *Lancet*, **375**(9716), 773–5.
36. **Gagnon B**, **Lawlor PG**, **Mancini IL**, **Pereira JL**, **Hanson J**, **Bruera ED** (2001) The impact of delirium on the circadian distribution of breakthrough analgesia in advanced cancer patients. *J Pain Symptom Manage*, **22**(4), 826–33.
37. **Fainsinger RL**, **Tapper M**, **Bruera E** (1993) A perspective on the management of delirium in terminally ill patients on a palliative care unit. *J Palliat Care*, **9**(3), 4–8.
38. **Breitbart W**, **Gibson C**, **Tremblay A** (2002) The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. *Psychosomatics*, **43**(3), 183–94.
39. **Hshieh TT**, **Yue J**, **Oh E** *et al.* (2015) Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA Intern Med*, **175**(4), 512–20.

40. **Agar MR**, **Lawlor PG**, **Quinn S** (2017) Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial. *JAMA Intern Med*, **177**(1), 34–42.
41. **Neufeld KJ**, **Yue J**, **Robinson TN**, **Inouye SK**, **Needham DM** (2016) Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: a systematic review and meta-analysis. *J Am Geriatr Soc*, **64**(4), 705–14.
42. **Bush SH**, **Tierney S**, **Lawlor PG** (2017) Clinical assessment and management of delirium in the palliative care setting. *Drugs*, **77**(15), 1623–43.
43. **Victoria Hospice Society** (2001) *Palliative Performance Scale (PPSv2), version 2*. http://www.npcrc.org/files/news/palliative_performance_scale_PPSv2.pdf
44. **Breitbart W**, **Marotta R**, **Platt M** *et al.* (1996) A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry*, **153**(2), 231–7.
45. **National Institute for Health and Care Excellence.** *Delirium: prevention, diagnosis and management*. Clinical guideline [CG103]. https://www.nice.org.uk/guidance/CG103
46. **Lawlor PG**, **Rutkowski N**, **MacDonald AR** *et al.* (2019) A scoping review to map empirical evidence regarding key domains and questions in the clinical pathway of delirium in palliative care. *J Pain Symptom Manage*, **57**(3), 661–81.e12.

Chapter 13

Anxiety and depression

Madeline Li, Gilla K. Shapiro, and Gary Rodin

Attitude

To enable each learner to:

- Understand the impact of emotional distress on quality of life and medical outcomes.
- Consider a biopsychosocial approach to understanding and treating emotional distress.
- Reflect on the continuum from normative distress to psychiatric disorders in palliative care.

Skills

To enable each learner to:

- Diagnose and manage anxiety and depression in palliative care.
- Demonstrate effective communication in responding to patients' distress.
- Integrate knowledge of pharmacological agents and psychosocial interventions in order to select treatments for anxiety and depression in palliative care.

Knowledge

To enable each learner to:

- Describe the incidence of mood and anxiety disorders in palliative care.
- Recognize the importance of interprofessional collaborative care when treating anxiety and depression in palliative care.
- Diagnose and treat anxiety and depressive disorders in palliative care.

Introduction

Disease progression is often associated with anxiety and depression on a continuum from normative distress to psychiatric illness. This chapter will illustrate, through case examples, the art and science of diagnosing and managing anxiety and depression in patients with palliative care needs.

Prevalence of, and risk factors for, anxiety and depression in palliative care

Studies in palliative care settings have found anxiety and depressive disorders in 10% and 25% of patients, respectively.[1] Sub-threshold symptoms that do not meet full diagnostic criteria for these disorders are even more common. Claims have been made that rates are higher in some medical conditions, but the prevalence of clinically significant symptoms varies more with the degree of disability, physical distress, and proximity to death.

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Clinical significance of untreated anxiety and depression

Anxiety in the palliative care setting is associated with physical symptoms such as fatigue, pain, and dyspnoea.[2] Individuals who tend to be anxious may have less confidence in their medical team[3] and have greater difficulty asking questions about their medical situation and understanding information presented to them. *Depression* in patients with advanced disease may limit their participation in end-of-life care, impair quality of life, and contribute to their wish to hasten death and suicide.[4] Untreated depression may also amplify pain and be associated with a twofold increase in healthcare utilization,[5] with poor self-care and reduced survival in advanced cancer.[6]

Case 13.1

A.G. is a 63-year-old former retail business manager with stage IV non-small cell lung cancer (NSCLC), with no remaining active cancer treatment options, who was referred to the palliative care service for treatment of progressive symptoms. His estimated prognosis is less than 6 months and his disease has prevented him from working for the past year. He and his partner of 15 years worry about how they will earn enough to provide for themselves. They share responsibility for A.G.'s daughter, a single mother with a 4-year-old son. A.G. was married in his twenties, but this marriage ended shortly after the death of their two-year-old son from a viral illness.

A.G. now spends much of his day on the sofa. His cough interferes with his sleep and when he wakes in the early morning, he is unable to fall back to sleep. His appetite is poor and he has lost 9 kg in weight. He feels unable to visit his grandson or to read, activities that had previously given him great pleasure. He had been an active, independent, and supportive caregiver to his partner but now feels that he is a burden to her. He is easily irritated by her worry about him and by her constant encouragement for him to eat. He fears becoming more helpless and dependent on his partner and states that he intends to move to a hospice when he can no longer use the bathroom independently. He feels despondent and profoundly fatigued, not having the energy to get out of bed in the morning. He says, with regret, 'My travelling days are over' and 'There is nothing left for me to enjoy'.

For the past month or more, his partner has noticed that A.G. has been more tearful and withdrawn. He has said to his physician, 'I can't live like this'. On several occasions, after a long and frustrating day, he has expressed thoughts of wanting to go to sleep and not wake up. He now thinks about his deceased son 'every day', although he does not like to talk about him to anyone.

In addition to his NSCLC, A.G. suffers from hypertension and hypothyroidism. His current medications include levothyroxine, ramipril, and codeine. He drinks alcohol only rarely and has never used street drugs. He was treated with antidepressants for depression almost 40 years ago following his son's death. A.G.'s mother had suffered from a major depressive disorder and his father from an alcohol use disorder.

A.G. walks and moves slowly and his speech is constantly interrupted by coughing. He slouches in his chair, with a downcast gaze, and speaks in short sentences. He appears dysphoric and sad and shows minimal range of facial expressions, with silent tears at several points in the interview.

Question 1. What psychiatric diagnoses would you consider for A.G.?

A.G.'s symptoms appear to be due both to the biological effects of his cancer and to a comorbid depressive disorder. His depression is severe and persistent enough to meet the diagnostic criteria for a major depressive episode (MDE), according to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)*.[7] The *core symptoms* of MDE in *DSM-5* are either a depressed mood or a loss of pleasure or interest in most activities

(i.e. anhedonia). Although transient feelings of this kind are common in patients with advanced disease, the diagnosis of MDE should be considered when they are present nearly every day, most of the day, for over 2 weeks, as in the case of A.G. This diagnosis requires the presence of one core symptom and at least five total symptoms. These include significant changes in weight or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, decreased energy, feelings of worthlessness or guilt, difficulty concentrating, and recurrent suicidal ideation or suicidal attempt. These criteria provide a framework for diagnosis, but clinical interventions require an understanding of the unique circumstances and psychology of the patient and to what extent these symptoms cause impairment in functioning (e.g. socially or occupationally).

In the diagnosis of MDE, the *DSM-5* adopts an aetiological approach, specifying that symptoms that are the direct result of a general medical condition do not count in the diagnosis. However, symptoms of a medical condition are not easily distinguished from those of depression. It requires experienced clinical judgement to determine whether symptoms such as poor appetite, sleep, energy, or concentration, and even sadness or thoughts of dying, are due to the medical condition or to comorbid depression. Loss of appetite may be due to depression or may be secondary to nausea, poor gastric motility, medications, or an active dying process. Impaired concentration and fatigue may be due to depression or to the effects of opioids, brain dysfunction, or disease-related fatigue. Disease-related fatigue may be less in the morning, increasing by evening as reserves are depleted. In contrast, depression-related anergia is often part of a circadian rhythm shift, with more energy in the morning than later in the day. Similarly, a circadian rhythm shift resulting in terminal insomnia (i.e. waking in the early morning hours and being unable to return to sleep) is more specific to depression than in so-called initial or middle insomnia.

A.G. manifests all of the criteria of MDE, and his poor morning energy, terminal insomnia sleep, impaired concentration, and psychomotor slowing are all disproportionate to the physical effects of his cancer. When making the diagnosis, particular attention should be paid to core psychological symptoms of dysphoria, anhedonia, and pessimism, as these have been found to be the most pathognomonic of depression in palliative care.[8] These are all present in A.G. who reports a persistently depressed mood and disinterest in formerly pleasurable activities on a near-daily basis and ruminative regrets and the wish that life were over.

MDE (*major depressive disorder*) may present as a discrete or recurrent unipolar disorder or as part of a *bipolar disorder in which there are manic or hypomanic episodes that precede or follow MDEs*. Other diagnoses that should be considered are listed below:

- Persistent depressive disorder. Chronic low-grade depressive symptoms or MDE continuously present for at least 2 years.
- Depressive disorder due to another medical condition. When the medical illness is considered to be the main direct cause of the depressive symptoms.
- Substance/medication-induced depressive disorder. When the effects of intoxication or withdrawal from a substance are considered to be the main cause of the depressive symptoms.
- Adjustment disorder. An emotional or behavioural reaction within 3 months of an identifiable stressor that either is excessive or causes significant impairment in functioning. Although not considered a depressive disorder in DSM-5, subtypes are specified as *with depressed mood*, *with anxiety*, or *with mixed anxiety and depressed mood*.

A.G.'s previous history of depression suggests that he suffers from a recurrent unipolar major depressive disorder. His personal and family history of mood disorders puts him at risk for this disorder, but since his medical condition undoubtedly is the most important contributor to his current depressive symptoms, the diagnosis of *depressive disorder due to another medical condition*

can be considered. In that context, specific biological contributors to his mood disturbance, such as hypothyroidism or other metabolic disorders, may also need to be ruled out.

Question 2. Is sadness a normal part of the process of dying?

Sadness is part of the normal human reaction to the multiple losses associated with a progressive and fatal disease. Some argue that normative grief can include all of the symptoms of MDE, and that normal sadness should not be pathologized. However, when low mood, anhedonia, hopelessness, or suicidal ideation are persistent and pervasive, the provision of appropriate psychological or psychiatric interventions could significantly improve the patient's quality of life.

Question 3. How would you understand A.G.'s wish to go to sleep and not wake up? How would you approach patients who express a wish to hasten death?

Transient thoughts that life might not be worth living and the wish to hasten death (WTHD) are common in patients with advanced disease. In assessing a patient's desire for death, it is important to distinguish thoughts from requests and intentions. Research suggests that an expressed desire to die may reflect a state of despair, but it may also represent an attempt at cognitive mastery by viewing death as a hypothetical exit plan or a non-pathological acceptance of death.[9]

The desire for hastened death or WTHD has been defined as a reaction to suffering in which the patient considers accelerating his or her death.[10] It is distinct from depression and demoralization syndrome[11] and may be a communication of despair warranting psychosocial intervention. It is also distinct from the intention to take action to end life, either in the form of rational requests for assisted dying or suicidality driven by mental disorders.

The legalization of assisted dying in many countries may affect how clinicians approach the expression of the WTHD. An American study of 1000 patients with advanced disease found that 10% had considered assisted death, but half of them had changed their minds within 6 months.[12] Patients with depressive symptoms in that study were five times more likely to consider assisted death than non-depressed individuals.[12] Similarly, a 2011 systematic review found a high prevalence of depressive symptoms in patients requesting assisted dying and in those receiving it.[13] In countries that offer assisted death, it is extremely important for clinicians to distinguish between a WTHD that is 'rational' and one that may be related to a depressive disorder.

For patients such as A.G., the first therapeutic step is to provide time and space to allow thoughts, including those about the WTHD, to be explored. Acknowledging and validating their distress and listening to their concerns and fears are essential to establish a therapeutic relationship and to bring relief. This may also include exploring the patient's fears about the future and about the end of life. Helping patients communicate their distress to their medical team will allow for the most appropriate therapeutic interventions. Alleviating the distress of patients and families may involve consultation with the interprofessional team, including nursing, psychiatry, psychology, social work, and spiritual care.

Question 4. How would you assess suicidality?

One of the most important roles of the clinician is to assess suicidal ideation and patient safety. The incidence of suicide among cancer patients is four times higher than in the general population[14]

and this risk is highest with advanced disease. Male patients, older at diagnosis and with certain cancers, such as lung, stomach, and head and neck cancers, are at higher risk.[15] Suicide risk assessment tools, such as the Suicide Assessment Five-Step Evaluation and Triage (SAFE-T),[16] can be useful. If there is a high risk of suicide, admission to a mental health unit or to a medical or palliative unit may be warranted. If involuntary admission is required, explaining to the patient and their family the importance of protecting the safety of the patient in these circumstances is important.

Question 5. What modifiable factors could be contributing to A.G.'s depressed mood?

Depression is the final common pathway of a range of biological, psychological, and social factors.[17] Identifying potential contributing factors can be a useful guide to investigation and treatment (see Table 13.1).[18] For A.G., investigating potential biological contributing factors involves symptom review and basic biochemical tests to rule out conditions such as anaemia, malnutrition, or hypothyroidism. Maximizing treatment of physical symptom burden, with attention to pain control, reversible causes of fatigue, cough, and insomnia, is imperative.

Having always been independent, A.G. is uncomfortable depending on others and is worried his healthcare team will not be available when he needs them. Psychological therapies may be helpful in addressing A.G.'s fears of dependency and his adjustment to the multiple losses that have occurred. He frequently worries about finances, medication coverage, and dying alone and in pain. Referral to a social worker for assistance with home care support and financial and end-of-life planning may be helpful.

Table 13.1 Factors that contribute to anxiety and depression[18]

Biological factors	Psychosocial factors
Physical burden of symptoms	Psychological factors
Pain, nausea	Attachment security
Fatigue, insomnia	Existential concerns
Dyspnoea	Coping strategies
Reversible medical conditions	Expectations of, and fears about, the future
Delirium	Loss of identity and/or dignity
Thyroid abnormalities	Increasing dependence on others
Vitamin B12 deficiency	Life stage
Metabolic abnormalities (e.g. electrolytes, glucose, hypercalcaemia)	Previous trauma
	Grieving losses
Medication use/withdrawal	Death awareness
Corticosteroids	Social factors
Cytokines (interferon-alpha, interleukin-2)	Communication with treatment team
Gonadotropin-releasing hormone agonists	Social support
Substance use/withdrawal	Role changes
Alcohol	Unresolved conflict in relationships
Nicotine	Concern about dependants or partner
Street drugs	Caregiver burnout and family distress
	Financial problems
	Practical and day-to-day support
	Planning for the future

Source: data from Li M, Boquiren VM, Lo C, Rodin G. 'Depression and anxiety in supportive oncology'. In *Supportive Oncology*, edited by Mellar Davis, Petra Feyer, Petra Ortner, Camilla Zimmermann. (Philadelphia, PA: Elsevier Saunders, 2011), p. 528–540.

Question 6. What are the pharmacological treatments for depression in palliative care?

Pharmacologic management of depression in patients with advanced disease can be extrapolated from evidence-based depression management guidelines published by The Canadian Network for Mood and Anxiety Treatments.[19] It should be noted that the therapeutic effects of antidepressant medication may take up to 8 weeks to deliver partial or full benefit, which may limit their utility near the end of life. Psycho-stimulants, such as methylphenidate and dexamphetamine, have been used in the treatment of depression in the palliative care setting, although their antidepressant effect has not been confirmed in randomized controlled clinical trials.[20] These rapid-acting agents can also improve fatigue, although they may exacerbate anxiety, anorexia, and sleep difficulties. More recently, evidence has been accumulating on the role of psychedelics, including psilocybin, 3,4-methylenedioxymethamphetamine (MDMA), and ketamine, for depression and psychological distress in palliative care because of their rapid onset of action.[21] However, access to psychedelic treatment is limited in most countries because of the limited evidence base to demonstrate their effectiveness. An exception is ketamine, which has recently received Food and Drug Administration (FDA) approval in the United States. Ketamine is an established pain and anaesthetic agent that can be used off-label for the treatment of depression. It has been shown in 11 separate trials to have rapidly acting antidepressant effects in palliative care populations, independent of its effects on pain.[22]

When considering antidepressant medication, the family history of response to treatment, side-effect profile, and drug–drug interactions are relevant considerations. The first-line drug in the treatment of major depression is usually a selective serotonin reuptake inhibitor (SSRI) or a serotonin–noradrenaline (norepinephrine) reuptake inhibitor (SNRI). Sertraline, citalopram, and escitalopram have the lowest levels of drug–drug interactions. Overall, SSRIs and SNRIs are well tolerated and safer in overdose than the older classes of antidepressants. Patients should be advised about the common short-term side-effects of headache, sedation or activation, hyponatraemia in the elderly, gastrointestinal upset at the time of treatment initiation, and withdrawal effects with abrupt discontinuation.

Careful monitoring is required after treatment initiation, as suicidal ideation can increase, particularly in adolescents or young adults. Attention should also be paid to the development of signs of serotonin syndrome,[23] which can occur if SSRIs or SNRIs are given along with other serotonergic medications commonly used in palliative care such as fentanyl, tramadol, metoclopramide, or ondansetron. Although rare, the signs of serotonin toxicity include acute autonomic instability, dilated pupils, confusion, neuromuscular features (e.g. tremor, rigidity, myoclonus, hyper-reflexia), sweating, and diarrhoea. When manifest with fever, convulsions, and coma, serotonin syndrome can be life-threatening. Management includes discontinuation of all serotonergic agents, close monitoring, and supportive care until symptoms resolve.

The side-effects of some agents, which are undesirable in the general population, may be useful in the palliative care setting. Bupropion may be particularly beneficial for patients with prominent symptoms of fatigue, hypersomnia, or psychomotor retardation due to its activating properties. Mirtazapine may stimulate appetite and promote sleep. When adding an agent to the patient's drug regimen, it is important to minimize the risk of drug–drug interactions and exercise caution about polypharmacy.

Although atypical antipsychotics have proven effectiveness in the treatment of bipolar disorder and as an adjunct in unipolar depression,[18] their role in treating mood symptoms in medically ill patients has not been established.[24] They are not recommended as first-line treatment for depressive symptoms in this population.

Question 7. What are the psychosocial treatments for depression in patients with palliative care needs?

The benefits of simple interventions, such as empathic listening, in reducing distress should not be underestimated. Helping patients navigate the healthcare system to meet their healthcare needs can also relieve distress. Recent narrative[25] and meta-analytic reviews[26] of psychotherapeutic interventions in palliative care demonstrate large effects in reducing depression, moderated by the type and intensity of therapies. Recent evidence from large randomized controlled trials (RCTs) has shown that meaning-centred therapy (MCT)[27] and a type of supportive–expressive therapy, referred to as Managing Cancer and Living Meaningfully (CALM),[28] are effective in alleviating depressive symptoms in patients with advanced cancer. However, a recent large RCT did not find benefit for cognitive behavioural therapy (CBT) in patients with advanced cancer.[29]

Psychotherapy may enable patients to communicate their distress and to find meaning in their experience. Such interventions help patients to explore feelings related to the disease, the threat of mortality, and the inevitable alterations in relational needs. A psychotherapeutic relationship may also help patients grieve past and anticipated losses. The relationship with a therapist may be particularly meaningful for patients at the end of life who are often highly motivated to address and resolve psychological problems.[30]

Case 13.1 (continued)

A.G. met with a social worker and received drug benefit coverage. He was started on sertraline titrated to 150 mg per day and began meeting with a therapist for supportive psychotherapy. During those sessions, he reflected on his life achievements and on creating a legacy for his grandson. His partner participated in some of the sessions, in which they discussed and negotiated the changes in their relationship that the illness had imposed and how they might adjust to A.G.'s progressive debility.

Following assessment and treatment, A.G.'s mood improved and he felt less fatigued and no longer overwhelmed. His thyroid-stimulating hormone (TSH) level, although slightly elevated, normalized with an increase in levothyroxine. Since his referral to the interprofessional palliative care team, his pain and cough had diminished. He experienced significant relief from the home care support team and was able to plan his will with his family and choose potential hospice locations.

Case 13.2

C.H. is a 52-year-old married mother of three young adult children. She emigrated from Latin America as a young adult and worked in a small dry cleaning business with her husband until her cancer onset. She has been living with metastatic breast cancer for 6 years and has had several courses of radiation and chemotherapy. She is now receiving palliative radiation therapy for bone metastases and is being cared for by the palliative care team. Mobility is significantly reduced due to moderate hip pain. She ambulates with a walker but has difficulty managing the stairs to her third-floor apartment. She was recently started on hydromorphone.

Over the last 6 weeks, as C.H.'s mobility has decreased, she has been feeling more anxious and worried about being alone. She has started waking in the night with intense fear, palpitations, tremulousness, sweating, and shortness of breath. These episodes last for 20–30 minutes and are relieved when she wakes her husband who comforts her. She cannot identify specific triggers for her anxiety but relates it to uncertainty about her future. If alone, she experiences significant worry about having outbursts that she will not be able to control. She also worries about being a burden on her family. Until now, C.H. has never perceived herself as a worrier, 'I was always the strong one—nothing bothered me'. Apart from her anxiety, she describes her

mood as stable and denies feeling overly sad or despondent. She enjoys the time she spends with her family, has a normal appetite, and has better pain control. Her family describes her as lucid and denies that she has had any periods of confusion or disorientation. They are struggling with how to help and are currently taking shifts to be with her, so that she is never alone.

C.H. has asthma, gastro-oesophageal reflux, hypertension, dyslipidaemia, and borderline diabetes. Her medications include hydromorphone, losartan, rosuvastatin, prednisone, pantoprazole, and lorazepam 1 mg nightly for sleep. She has no known psychiatric history and does not drink alcohol, use street drugs, or smoke.

Question 8. How would you characterize C.H.'s symptoms of anxiety?

C.H. is experiencing what appear to be panic attacks, triggered by fears of dying alone. These are distinct episodes of intense anxiety, generally lasting for a period of minutes, that peak within 10 minutes and are characterized by four or more of the following symptoms: chills, diaphoresis, derealization/depersonalization, fear of loss of control or sanity, fear of dying, shaking, paraesthesiae, light-headedness, nausea, dyspnoea, chest tightness, choking, or palpitations.

Panic attacks consist of a cluster of symptoms that can be associated with anxiety disorders, adjustment disorders, or depression, although they may also occur in isolation. The categorization of relevant anxiety disorders in DSM-5 includes *substance/medication-induced anxiety disorders* and *anxiety disorder due to another medical condition*, in addition to the diagnoses listed below, which may be of relevance in palliative care:

- Panic disorder. The presence of recurrent and unexpected panic attacks with at least 1 month of persistent worry about having another panic attack, or worry about the consequences of the attack, or a significant change in the individual's behaviour due to the panic attacks.
- Specific phobia. Significant and persistent fear in response to specific objects or situational triggers that is out of proportion to the actual danger that is posed. Panic attacks can occur related to fear of needles, blood, invasive medical procedures, or being enclosed in small spaces such as imaging scanners or radiation masks.
- Generalized anxiety disorder (GAD). Characterized by excessive and uncontrollable worry about many different things on most days for at least 6 months, associated with restlessness, fatigue, difficulty concentrating, muscle tension, or sleep disturbance. Those with GAD may have identified themselves as 'a worrier by nature' and may catastrophize, experiencing unrealistic fears about their illness, their treatment, or its impact on their daily lives.
- Other specified anxiety disorder. This refers to anxiety symptoms that do not fit clearly into a diagnostic category. Anticipatory anxiety and conditioned nausea and vomiting[31] could fall within this category.
- Trauma- and stressor-related disorders. While not considered anxiety disorders in *DSM-5*, panic attacks can also occur in the context of adjustment disorder, acute stress disorder (ASD), or post-traumatic stress disorder (PTSD).[32] PTSD can occur after an individual has experienced a serious trauma (ASD if within 1 month), with associated symptoms of intrusive memories, avoidance of reminders, negativity, and hyperarousal. DSM-5 now specifies that a life-threatening illness only qualifies as a trauma if it involves a sudden, catastrophic event. This may be more likely to occur with diseases such as haematological malignancies, which may be sudden in their onset and punctuated by dramatic changes in clinical status.

Diagnoses to consider in the case of C.H. include panic attacks associated with *anxiety disorder due to another medical condition*, a *substance/medication-induced anxiety disorder*, panic disorder, or adjustment disorder with anxiety.

Question 9. How would you approach treatment of C.H.'s anxiety?

It is important to adopt a multi-system approach to C.H.'s anxiety that considers general medical causes, drug effects, and fears about disease progression and abandonment (see Table 13.1). Optimizing pain control and considering pharmacological agents to treat anxiety are important.[33] Although benzodiazepines are generally first-line treatment and are effective anxiolytic agents for short-term situational anxiety, they should be used cautiously in lung disease due to the risk of respiratory depression. They have also been associated with falls in the elderly and with exacerbation of delirium and confusion. The use of benzodiazepines is optimally limited to the treatment of acute panic attacks or specific treatment-related phobias. If hepatic function is impaired, preference should be given to lorazepam, oxazepam, or temazepam, as their metabolism by phase II glucuronidation is less dependent on liver metabolism. For panic attacks that are severe, frequent, or interfering with daily functioning, SSRIs are considered to be first-line treatment, although they may take several weeks to become effective. SSRIs should be initiated at half the usual starting dose, as the initial side-effects of nausea and dizziness can precipitate panic attacks and result in treatment discontinuation. In general, antidepressant medications, such as tricyclic antidepressants (TCAs), SSRIs, and SNRIs, have been shown to have anxiolytic effects for anxiety disorders, including GAD and PTSD. Buspirone, a non-benzodiazepine anxiolytic without sedative or cognitive side-effects, can be used in the treatment of GAD, and atypical neuroleptics, such as risperidone, olanzapine, and quetiapine, can be used as adjunctive agents in PTSD. Antipsychotic agents are not recommended as a first-line treatment for anxiety in palliative care, although they are often used in this setting for other indications.

From a psychosocial perspective, attention to C.H.'s physical situation may be helpful. This may involve having an occupational therapist assist with her mobility needs, installing a medical alert system to reassure her about the availability of help in the case of an emergency, connecting her or her family to support groups in the community, or having volunteers from a hospice or community agency meet with her at home. These interventions may diminish her sense of vulnerability and alleviate perceived and actual caregiver burden. Deep breathing, visual imagery, or progressive relaxation strategies can be effective for aborting panic attacks and reducing anxiety. This may include 'box breathing', which involves imagining repeatedly tracing the four sides of a square while slowly breathing in and out, with breath-holding in between. The evidence is strongest for the effectiveness of CBT in treating panic disorder, with response rates equivalent to those for antidepressants. Psychotherapies designed to treat other anxiety disorders include CBT, mindfulness-based stress reduction (MBSR), and supportive psychotherapies. CBT and relaxation techniques can be particularly helpful for patients with anticipatory nausea and vomiting and specific phobias related to treatment.

Case 13.2 (continued)

C.H. was started on escitalopram 10 mg in the morning and lorazepam 0.5 mg daily as needed. She learned relaxation and breathing techniques to use when she felt overwhelmed. Over the next few weeks, she used lorazepam less and felt less overwhelmed. Night awakenings resolved, and she only had the occasional sense of distress during the day. Her family installed a safety system and the nurses checked in on her regularly. Her

pain was managed, and her flat modified to accommodate a wheelchair. She felt less vulnerable and was able to start talking to her nurse about her anxieties and fears.

Case 13.3

Y.L. is a 51-year-old divorced engineer now on disability income. He lives alone. He was diagnosed with end-stage interstitial lung disease and recently developed secondary pulmonary hypertension. He has been on home oxygen therapy for the last few years. He does not qualify for lung transplant. He has always understood that his disease is incurable and managed to keep busy and avoid thinking about his prognosis. He had maintained a positive, hopeful attitude until his disease progressed and he was given a prognosis of less than 6 months. Since then, he has been increasingly distressed about dying alone in his home. He spends his days calling his family in tears but cannot articulate what he is tearful about. When his family is with him, he reports a sense of well-being and takes pleasure in their visits. He enjoys distracting activities such as reading, playing the piano, and watching hockey. He denies problems with his appetite and concentration, or feelings of hopelessness or guilt. He does not experience panic attacks or persistent anxiety, but has difficulty being alone with his thoughts, and keeps the radio or television on at all times. He has had great difficulty with initial insomnia.

His family has not been able to engage him in completing his will or discussing an advance directive or funeral arrangements. During the last week, he has turned away home care support staff and missed an appointment with his medical team.

Question 10. What is your impression of how Y.L. is coping?

Y.L. is experiencing significant distress, although his symptoms do not meet the criteria for the diagnosis of an anxiety or depressive disorder. He has a notable impairment in his attention to his medical care and important end-of-life planning. His presentation is most consistent with the diagnosis of an adjustment disorder with mixed anxiety and depressed mood. Although the diagnosis of adjustment disorder lacks specificity, it is the most common psychiatric diagnosis in medically ill patients. Its validity has been debated, but most agree that it has clinical utility in capturing prodromal or transient states of distress in a way that is not stigmatizing.[34]

Question 11. How would you provide intervention for such emotional distress?

Approaches for relieving distress or treating adjustment disorders are best tailored to the patient's situation. Psychological interventions are generally the first line of treatment for adjustment disorders, with the primary goal of reducing the severity of stressors, enhancing coping skills, and strengthening the available support system. They can include a wide range of psychological interventions, such as education, relaxation, guided imagery, music therapy, and individual, family, or group therapies.[35] Medications may be indicated for patients with adjustment disorder who are not benefiting from supportive measures or psychotherapy.[36] The use of medications for insomnia, anxiety, or depressive symptoms may be helpful, particularly if drugs are selected that may also alleviate related physical symptoms.

Sub-threshold distress management does not necessarily require specialist psychosocial intervention, and some patients will not accept it in any case. The medical team can alleviate

psychological distress by establishing a supportive relationship, addressing pain and symptom control, and communicating in a way that maintains morale.[37]

Case 13.3 (continued)

Y.L. adamantly refused referral for supportive counselling for himself. Psychiatric liaison helped the medical team and Y.L.'s family to understand his tendency to dismiss his need for support, to accept his desire not to discuss his prognosis, and to understand his preference for problem-focused coping. Planning for eventual placement on a palliative care unit relieved much of his distress about dying alone at home. Zopiclone was helpful for his sleep, and over the next month, his distress gradually subsided.

Summary

The bidirectional relationship between psychological and physical distress highlights the importance of integrated psychosocial and palliative care provided by interprofessional, collaborative care teams. Pain and symptom control, supportive communication, and advanced care planning may all relieve distress in patients with advanced disease. However, specialized psychotherapeutic and pharmacological interventions may also be needed to relieve more persistent symptoms of depression and anxiety and to sustain the will to live. Although anxiety is common at the time of diagnosis, recurrence or when awaiting or receiving test results, depression tends to be a more cumulative response to disease progression, both may be diminished or prevented by psychosocial interventions.

References

1. **Mitchell AJ, Chan M, Bhatti H** *et al.* (2011) Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care setting: a meta-analysis of 94 interview based studies. *Lancet Oncol*, **12**, 160–74. doi: 10.1016/S1470-2045(11)70002-X
2. **Delgado-Guay M, Parsons HA, Li Z, Palmer JL, Bruera E** (2009) Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting. *Support Care Cancer*, **17**, 573–9. doi: 10.1007/s00520-008-0529-7
3. **Spencer R, Nilsson M, Wright A, Pirl W, Prigerson H** (2010) Anxiety disorders in advanced cancer patients: correlates and predictors of end-of-life outcomes. *Cancer*, **116**, 1810–19. doi: 10.1002/cncr.24954
4. **Rodin G, Zimmermann C, Rydall A** *et al.* (2007) The desire for hastened death in patients with metastatic cancer. *J Pain Symptom Manage*, **33**, 661–75. doi: 10.1016/j.jpainsymman.2006.09.034
5. **Li M, Rodin G** (2011) Depression. In: Levinson JL (ed.) *Textbook of Psychosomatic Medicine: Psychiatric Care of the Medically Ill*, 2nd edn, pp. 175–97. American Psychiatric Publishing, Arlington, VA.
6. **Lloyd-Williams M, Payne S, Reeve J, Dona RK** (2014) Thoughts of self-harm and depression as prognostic factors in palliative care patients. *J Affective Disord*, **166**, 324–9. doi: 10.1016/j.jad.2014.05.029
7. **American Psychiatric Association** (2013) *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, 5th edn. American Psychiatric Association, Washington, DC.
8. **Huey NS, Guan NC, Gill JS, Hui KO, Sulaiman AH, Kanagasundram S** (2018) Core symptoms of major depressive disorder among palliative care patients. *Int J Environ Res Public Health*, **15**, 1758. doi: 10.3390/ijerph15081758
9. **Nissim R, Gagliese L, Rodin G** (2009) The desire for hastened death in individuals with advanced cancer: a longitudinal qualitative study. *Soc Sci Med*, **69**, 165–71. doi: 10.1016/j.socscimed.2009.04.021

10. **Balaguer A, Monforte-Royo C, Porta-Sales J** *et al.* (2016) An international consensus definition of the wish to hasten death and its related factors. *PLoS ONE*, **11**, e0146184. doi: 10.1371/journal.pone.0146184
11. **Grassi L, Nanni MG** (2016) Demoralization syndrome: new insights in psychosocial cancer care. *Cancer*, **122**, 2130–3. doi: 10.1002/cncr.30022
12. **Emanuel EJ, Fairclough DL, Emanuel LL** (2000) Attitudes and desires related to euthanasia and physician-assisted suicide among terminally ill patients and their caregivers. *JAMA*, **284**, 2460–8. doi: 10.1001/jama.284.19.2460
13. **Levene I, Parker M** (2011) Prevalence of depression in granted and refused requests for euthanasia and assisted suicide: a systematic review. *J Med Ethics*, **37**, 205–11. doi: 10.1136/jme.2010.039057
14. **Zaorksy NG, Zhang Y, Tuanquin L, Bluethmann SM, Park HS, Chinchilli VM** (2019) Suicide among cancer patients. *Nat Commun*, **10**, 207. doi: 10.1038/s41467-018-08170-1
15. **Filiberti A, Ripamonti C, Totis A** *et al.* (2001) Characteristics of terminal cancer patients who committed suicide during a home palliative care program. *J Pain Symptom Manage*, **22**, 544–53. doi: 10.1016/s0885-3924(01)00295-0
16. **Stop A Suicide Today**. https://stopasuicide.org
17. **Rodin G, Lo C, Mikulincer M, Donner A, Gagliese L, Zimmermann C** (2009) Pathways to distress: the multiple determinants of depression, hopelessness, and the desire for hastened death in metastatic cancer patients. *Soc Sci Med*, **68**, 562–9. doi: 10.1016/j.socscimed.2008.10.037
18. **Li M, Boquiren VM, Lo C, Rodin G** (2011) Depression and anxiety in supportive oncology. In: Davis M, Feyer P, Ortner P, Zimmermann C (eds.) *Supportive Oncology*, pp. 528–40. Elsevier Saunders, Philadelphia, PA.
19. **Kennedy SH, Lam RW, McIntyre RS** *et al.* (2016) Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. *Can J Psychiatry*, **61**, 540–60. doi: 10.1177/0706743716659417
20. **Andrew BN, Guan NC, Jaafar NRN** (2018) The use of methylphenidate for physical and psychological symptoms in cancer patients: a review. *Curr Drug Targets*, **19**, 877–87. doi: 10.2174/1389450118666170317162603
21. **Byock I** (2018) Taking psychedelics seriously. *J Palliat Med*, **21**, 417–21. doi: 10.1089/jpm.2017.0684
22. **Goldman N, Frankenthaler M, Klepacz L** (2019) The efficacy of ketamine in the palliative care setting: a comprehensive review of the literature. *J Palliat Med*, **22**, 1154–61. doi: 10.1089/jpm.2018.0627
23. **Foong A-L, Grindrod K, Patel T, Kellar J** (2019) Demystifying serotonin syndrome (or serotonin toxicity). *Can Fam Physician*, **64**, 720–7.
24. **Lam RW, Kennedy SH, Grigoriadis S** (2009) Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. *J Affect Dis*, **117**, S26–43. doi: https://doi.org/10.1016/j.jad.2009.06.041
25. **Rodin G, An E, Shnall J, Malfitano C** (2020) Psychological interventions for patients with advanced disease: implications for oncology and palliative care. *J Clin Oncol*, **38**, 885–904. doi: https//doi.org/10.1200/JCO.19.00058
26. **Fulton JJ, Newins AR, Porter LS, Ramos K** (2018) Psychotherapy targeting depression and anxiety for use in palliative care: a meta-analysis. *J Palliat Med*, **21**, 1024–37. doi: 10.1089/jpm.2017.0576
27. **Breitbart W, Pessin H, Rosenfeld B** *et al.* (2018) Individual meaning-centered psychotherapy for the treatment of psychological and existential distress: a randomized controlled trial in patients with advanced cancer'. *Cancer*, **124**, 3231–9. doi: 10.1002/cncr.31539
28. **Rodin G, Lo C, Rydall A** *et al.* (2018) Managing Cancer and Living Meaningfully (CALM): a randomized controlled trial of a psychological intervention for patients with advanced cancer. *J Clin Oncol*, **36**, 2422–32. doi: 10.1200/JCO.2017.77.1097

29. **Serfaty M, King M, Nazareth I** *et al.* (2019) Effectiveness of cognitive-behavioural therapy for depression in advanced cancer: CanTalk randomised controlled trial. *Br J Psychiatry*, **216**, 213–21. doi: https://doi.org/10.1192/bjp.2019.207
30. **Rodin G** (2009) Individual psychotherapy for the patient with advanced disease. In: Chochinov HM, Breitbart W (eds.) *Handbook of Psychiatry in Palliative Medicine*, 2nd edn, pp. 443–5. Oxford University Press, New York, NY.
31. **Aapro MS, Molassiotis A, Olver I** (2005) Anticipatory nausea and vomiting. *Support Care Cancer*, **13**, 117–21. doi: 10.1007/s00520-004-0745-8
32. **Cordova MJ, Riba MB, Spiegel D** (2017) Post-traumatic stress disorder and cancer. *Lancet Psychiatry*, **4**, 330–8. doi: 10.1016/S2215-0366(17)30014-7
33. **Roy-Byrne PP, Davidson KW, Kessler RC** *et al.* (2008) Anxiety disorders and comorbid medical illness. *Gen Hosp Psychiatry*, **30**, 208–5. doi: 10.1016/j.genhosppsych.2007.12.006
34. **Maercker A, Lorenz L** (2018) Adjustment disorder diagnosis: improving clinical utility. *World J Biol Psychiatry*, **19**, S3–13. doi: 10.1080/15622975.2018.1449967
35. **Domhardt M, Baumeister H** (2018) Psychotherapy of adjustment disorders: current state and future directions. *World J Biol Psychiatry*, **19**, S21–35. doi: 10.1080/15622975.2018.1467041
36. **Stein DJ** (2018) Pharmacotherapy of adjustment disorder: a review. *World J Biol Psychiatry*, **19**, S46–52. doi: 10.1080/15622975.2018.1492736
37. **Khan L, Wong R, Li M** *et al.* (2010) Maintaining the will to live of patients with advanced cancer. *Cancer J*, **16**, 524–31. doi: 10.1097/PPO.0b013e3181f45b90

Chapter 14

Grief and bereavement

Alexandra Farag

Attitude

To enable each learner to:

- Reflect on the critical role that healthcare providers play in a patient's and family's experience of grief and how they cope during their bereavement.

Skills

To enable each learner to:

- Recognize normal, anticipatory, and pathologic grief.
- Develop an approach to managing bereavement and grief in themselves.

Knowledge

To enable each learner to:

- Summarize the basic treatment strategies for complicated grief, depression, and related conditions.

Introduction

Grief is the normal reaction or response to the loss of a loved one such as the death of a partner friend, parent, sibling, or child. Grief can also be the response to the loss of relationship, dreams, hopes, abilities, and future opportunities. The state of having lost a loved one is called bereavement. It is a universal and highly stressful life experience. Like any stressor, bereavement is associated with an increased risk of developing mental and physical health problems.[1] Several studies have shown that bereaved individuals have higher rates of disability, drug use, and even mortality than their non-bereaved counterparts.[1,2] These complications have been shown to affect a select group of bereaved individuals disproportionately.[1,2,3,4] Given the negative health outcomes associated with bereavement, it is important for clinicians to have an approach to supporting patients who are grieving and intervening appropriately in pathological grief.

Case 14.1

Normal grief

S.G.'s husband A.G. died of amyotrophic lateral sclerosis when they were both 55-years-old. They were devoted to one another. S.G. vividly remembers the night of A.G.'s death. He was at the hospital, lying in bed,

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emaciated. His breathing slowed and he had long pauses in between his breaths. Then he stopped breathing. S.G. remembers feeling shocked after his death. Though she knew it was imminent, it was hard to comprehend that he was gone.

In the weeks after, she could think of nothing else. S.G. intensely longed for him and had trouble concentrating on other things. Her mind was in a fog. One night, S.G. woke suddenly and 'saw' A.G. standing at the foot of her bed. She worried about this experience and visited her family physician to talk about it.

Question 1. What is S.G. experiencing?

S.G. is grieving the loss of her husband. Grief is characterized by a number of physical, emotional, cognitive, and spiritual experiences (see Table 14.1).[5,6,7] These vary by cultural context and are influenced by personality, nature of the relationship with the deceased, preparation for death, importance of the loss, and support network.[5,7]

Several models have been proposed to explain how people grieve and come to terms with loss. The Phase or Stage Model of Grief describes a series of stages that bereaved individuals move through in order to cope with their loss. Bowlby and Parkes identified four stages of grief: shock–numbness, yearning–searching, disorganization–despair, and reorganization.[8,9] Elizabeth Kluber-Ross adapted this model into a 5-stage response to impending loss, which includes denial–dissociation–isolation, anger, bargaining, depression, and acceptance.[9,10] The Task Model of Grief describes four tasks that an individual must complete to move through grief. The tasks include

Table 14.1 Symptoms of acute grief

Physical	Chest pain Palpitations Insomnia Anorexia Fatigue Nausea
Emotional	Anxiety Sadness Fear Anger Guilt Apathy Relief
Cognitive	Difficulty concentrating Confusion Forgetfulness
Spiritual	Questioning god Re-evaluation of faith Searching for meaning

Source: data from Ringdal G, et al. 'The first year of grief and bereavement in close family members to individuals who have died of cancer'. *Palliat. Med*. Vol 15, Issue 2, pp. 91–105, 2001; Casarett D, et al. 'Life after death: A practical approach to grief and bereavement'. *Ann Intern Med*. Vol 134, Issue 3, pp. 208–215, 2001; and Pereira, J. 'The Pallium Palliative Pocketbook: a peer-reviewed, referenced resource', 2nd ed. Ottawa,ON: Pallium Canada; 2016.

accepting the reality of the loss, working through the pain of grief, adjusting to an environment in which the deceased is missing, and finding an enduring connection with the deceased while moving on.[11,12] Failing to move through these stages or complete the tasks can lead to complications.[10,11,12] The Dual Process Model of Grief describes grief as a process of moving between two states: 'loss orientation' and 'restoration orientation'.[11,13,14] Loss orientation focuses on expressing and understanding the range of emotional responses associated with the loss. Restoration orientation focuses on the many external adjustments required by the loss, including diversion from it and attention to ongoing life demands. The model suggests that coping may vary, based on time, individual, and cultural context.[11,13]

Question 2. As S.G.'s family physician, how do you respond?

The majority of bereaved individuals are able to move through their grief without medical intervention, and high-quality evidence supporting interventions in normal grief is lacking.[15] In many cases, support from family and friends is all that is needed to cope with the loss. In caring for S.G., it is important to be present and listen to her experience. S.G. is likely concerned that her symptoms are abnormal. Providing time and permission to grieve and the reassurance that her grief is normal will be comforting to her. As S.G.'s physician, you should also assess her social support and coping resources. If S.G. lacked social supports, additional grief counselling, online resources for grief, or self-help books may be beneficial for her.[6] A selection of resources is summarized in Table 14.2.

Case 14.1 (continued)

S.G.'s family physician reassured her that her experiences had been normal. She encouraged her to share her feelings with her social supports and booked a follow-up appointment to continue to discuss her loss. After 3 months, S.G. felt like the 'fog' was lifting. She was able to laugh again. After a year, her thoughts of A.H. diminished. She still missed him dearly but was able envision her life without him. She decided to go back to school, travel, and re-engage in her life.

Table 14.2 Grief and bereavement resources

Organization	Website	Description
Canadian Virtual Hospice	https://mygrief.ca	Series of confidential modules developed by grief experts to assist in moving through grief
Canadian Mental Health Association	https://cmha.ca	Handouts and resources about grief
Canadian Cancer Society	https://www.cancer.ca/en/region-selector-page/?url=%2fen%2f	Information and online forum to discuss cancer-related topics
Alzheimer's Society of Canada	https://alzheimer.ca/en	Webinars, modules, and volunteer programmes across Canada

Case 14.2

Anticipatory grief

J.R.'s spouse L.K. has been living with metastatic breast cancer for over 6 years. In the past 3 months, J.R. has noticed a significant decline in L.K.'s function. L.K. is no longer able to go to her weekly book club or take care of household tasks and she needs help with basic care. At L.K.'s most recent visit with her oncologist, scans showed that the cancer was getting worse and they decided not to continue with chemotherapy and instead focus on interventions for comfort and quality of life.

J.R. has been finding it hard to cope with L.K.'s illness. She knows L.K.'s time is short. J.R. spends most of her time thinking about L.K.'s care and her eventual death, and has not been participating in activities that she previously enjoyed. L.K. often finds J.R. crying at night. She worries about how J.R. is doing but does not know how to help her. At a follow-up visit with you, her primary care provider, she mentions this. She is concerned that J.R. might be experiencing anticipatory grief.

Question 3. You ask J.R. to come for her own appointment. How do you approach this visit?

When assessing J.R., it is important to rule out other causes of her symptoms, including an organic cause, major depressive disorder, or adjustment disorder. J.R. appears to be experiencing *anticipatory grief*, the process by which a person comes to terms with the impending loss of a loved one.[6] Anticipatory grief is a multidimensional syndrome consisting of anger, guilt, sadness, feelings of loss, and decreased ability to perform usual tasks.[16] It is strongly associated with increased caregiver burden[17] and is important to address to prevent caregiver burnout.

Offering support should be the main focus of managing anticipatory grief. Clarifying J.R. and L.K.'s illness understanding and knowledge about prognosis will be helpful, as well as exploring J.R.'s feelings and concerns. Acknowledging grief openly and encouraging J.R. and L.K. to discuss L.K.'s impending death can also provide comfort and strengthen their relationship. This discussion can also be supplemented with a life review, dignity therapy, or legacy work, which can be offered by spiritual care clinicians, social workers, or psychologists.[6]

Case 14.3

Complicated grief/depression

J.J. has been married to M.J. for over 50 years. They have been through many ups and downs together. J.J. met M.J. in high school and it was love at first sight. They married shortly after graduation. J.J. went on to work as a geography teacher. M.J. took care of the housework and raising their son T.J. When T.J. was 30 years old, he died suddenly of a drug overdose. J.J. and M.J. were devastated, and J.J. stopped working and went through a difficult period following T.J.'s death. After a few years, with counselling and M.J.'s support, J.J. was able to move through.

Five years later, M.J. was diagnosed with Alzheimer's dementia. The signs were subtle at first. M.J. began forgetting things when she went grocery shopping and her cooking started tasting a bit off. J.J. took on the household tasks and started to care for M.J. She gradually continued to decline, and J.J. began having more difficulty managing her care. One evening, when they were having supper, M.J. started to cough and became short of breath. She had been coughing after eating in the past, never this bad. J.J. called emergency medical services, and they rushed her to the hospital. She died shortly after arrival.

Question 4. What are J.J.'s risk factors for a complicated grief course?

Risk factors for a poor outcome following bereavement are summarized in Box 14.1. Individuals who have lost a child or spouse are at higher risk of complications following bereavement.[17,18] People who lose a loved one suddenly or unexpectedly are more likely to experience complicated grief than those who lose a loved one due a progressive life-limiting illness.[17,18,19,20,21] Men who lose a spouse are at higher risk of mortality following the death than women, whereas women who lose a spouse are at higher risk of depression.[19]

J.J.'s risk factors include his older age, his lack of social support, his relationship with M.J., and a history of comorbid psychiatric illness. Although M.J.'s death may have been expected to her healthcare providers, J.J. was not prepared for her death. M.J.'s death also may have triggered memories of the death of his son T.J. and the trauma of that experience. J.J.'s life changed dramatically following his wife's death. He had been her caregiver and had taken pride and meaning in the day-to-day tasks of caring for her. Following her death, he struggled with this loss of his previous role.

Box 14.1 Risk factors for poor outcome of bereavement

Predisposing factors

- Type of relationship:
  - Dependent relationship
  - Spouse
  - Parent
- Multiple prior losses
- Previous psychiatric illness
- Lower socio-economic status
- Older age
- Gender
- Lack of perceived social supports

Circumstances surrounding death

- Sudden and unexpected
- Preparation for the death
- Stigmatized death (overdose, suicide)
- Caring for the deceased person for over 6 months

Post-death

- Inability to perform religious rituals
- Loss resulting in major changes (loss of role, negative financial changes)

Case 14.3 (continued)

After M.J.'s death, J.J. was overwhelmed with feelings of despair, yearning, and longing for M.J. He felt disconnected from friends and family. It was hard to think about anything other than M.J. He ruminated about her death, convinced that it was his fault. He felt that if he had only taken better care of her, she would have been alive today. He thought that he had failed her. His life had no meaning without her.

Friends tried to support J.J., but he did not have the energy to see them. For almost 8 months, he spent his time at home, on his couch, watching TV. He was unable to sleep, eat, shop, or perform even the simplest task. He had no interest in doing anything. Eventually, J.J. began contemplating suicide. He felt that the world would be better off without him. He considered taking a cocktail of his wife's old pills but stopped himself because he worried he would never see her again. Concerned that his grief was becoming out of control, he decided to return her unused pills to the pharmacy and to see his family physician.

Question 5. What is the differential diagnosis for what J.J. is experiencing?

When assessing J.J., it is important to consider normal grief, adjustment disorders, depressive disorders, post-traumatic stress disorder (PTSD), and organic causes of his symptoms. Blood work, including complete blood count, thyroid-stimulating hormone (TSH), ferritin, B_{12}, creatinine, and liver enzymes, can help to rule out other causes of his symptoms such as anaemia or hypothyroidism.

Although J.J. believes his symptoms are consistent with grief, there are several signs that he is experiencing a major depressive episode. Grief is characterized by waves of feelings of emptiness and loss, which can be triggered by reminders of the deceased. On the other hand, in a major depressive episode, the depressed mood is persistent and pervasive.[22] Patients who are experiencing normal grief are preoccupied with thoughts and memories of the deceased, unlike patients with depression who often experience self-critical, pessimistic ruminations such as J.J.'s preoccupation that he could have 'saved' M.J. Thoughts of death and dying occur in both normal grief and depression. In grief, these thoughts are associated with joining the deceased, whereas in depression, these thoughts are focused on ending one's life because they feel worthless or undeserving of life.[22] J.J.'s suicidal ideation is more consistent with depression.

Adjustment disorder should also be included in the differential diagnosis. Adjustment disorder is defined by the development of marked distress in response to a stressor that is out of proportion to that stressor.[22] J.J.'s distress has persisted past the 6-month time period expected for adjustment disorder.

Bereaved family members who experience the traumatic death of a loved one may develop PTSD. PTSD is characterized by intrusive thoughts, hyperarousal, and avoidance of the traumatic event.[22] While J.J. is having intrusive thoughts, he is experiencing psychomotor depression, not hyperarousal, and rather than avoiding thoughts that remind him of the event, he is ruminating about them.

In this case, J.J.'s symptoms appear most consistent with a major depressive episode. Depression is common in the first year of bereavement. Overall estimates of depression in the first year following a loss range from 17% to 27%.[18] The previous iteration of the DSM, the DSM-IV, included a clause excluding recently bereaved persons from the diagnosis of major depressive disorder.[22] This was removed in the DSM-V. While bereavement is a major life event, it does not typically induce a major depressive episode. When bereavement and depression occur together, the depressive symptoms and functional impairment are more severe, compared with normal

bereavement.[22] Patients who are exhibiting symptoms of a major depressive episode should therefore be diagnosed with major depressive disorder, even if they are recently bereaved.

Question 6. After ruling out other causes of J.J.'s symptoms, you diagnose him with major depressive disorder. How can you help him?

J.J. should be reassured that his story will be heard in a safe and confidential environment. Given his suicidal ideation, his appointment should include a detailed safety assessment. His older age, gender, and lack of social support put him at a higher risk of completion of suicide.[23,24] However, he is seeking help and does not appear to have an active plan. Tools such as the Geriatric Suicide Ideation Scale[25] and the SAD PERSONS Scale[26] can help inform the clinician's risk assessment. If J.J. had been actively suicidal, with a plan and preparation, then hospital admission and inpatient treatment would be warranted.

The choice of therapy will depend largely on the personality and goals of the bereaved person. It is reasonable to prescribe multiple treatment options, including both pharmacologic therapy and psychotherapy. There are several antidepressants that can be used for major depressive disorder (see Table 14.3). The choice of antidepressive agent should be guided by the side-effect profile and patient comorbidities.[27] J.J. should be encouraged also to get out of the house, exercise, and try to engage in activities that he previously enjoyed. A referral to a psychiatrist, psychologist, or

Table 14.3 First-line agents for depression

Medication (brand name)	Mechanism	Dose range (mg)
Buproprion (Wellbutrin®)	NDRI	150–300
Citalopram (Celexa®)	SSRI	20–40
Desvenlafaxine (Pristiq®)	SNRI	50–100
Duloxetine (Cymbalta®)	SNRI	60
Escitalopram (Cipralex®)	SSRI	10–20
Fluoxetine (Prozac®)	SSRI	20–60
Fluvoxamine (Luvox®)	SSRI	100–300
Mirtazapine (Remeron®)	α2-adrenergic agonist; 5HT2 antagonist	15–45
Paroxetine (Paxil®)	SSRI	20–50
Sertraline (Zoloft®)	SSRI	50–200
Venlafaxine (Effexor®)	SNRI	75–225
Vortioxetine (Brintellix®, Trintellix®)	Serotonin reuptake inhibitor; 5HT1A agonist; 5HT1B partial agonist; 5-HT1D, 5HT3A, and 5HT7 antagonist	10–20

Table includes only agents that have been approved and are available in Canada.

NDRI, norepinephrine and dopamine reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Adapted with permisison from Kennedy S et al. 'Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the Management of adults with Major Depressive Disorder: Section 3. Pharmacological treatments'. *Can J Psychiatry*. Vol. 61, Issue 9. pp 540–60. Copyright (C) 2016 SAGE Publications.

counsellor for psychotherapy may also be beneficial.[28,29] Regardless of the treatment modality chosen, he will require close follow-up, given the severity of his symptoms.

Case 14.3 (continued)

J.J.'s physician listens to his story and encourages him to spend time with his friends. She starts J.J. on mirtazapine to help with his sleep, appetite, and mood, and refers him to the counsellor at their clinic. After a few weeks, J.J. begins to feel a bit better. J.J. enjoys his visits with the counsellor, as it allows him the opportunity to speak about M.J. With his counsellor's encouragement, J.J. decides to join a support group for widowed seniors. He eventually takes on a leadership role in the group and takes pride in supporting others who have gone through similar experiences.

Case 14.4

Grief in the healthcare team

Dr C.I. has been practising as a family physician for 30 years. One of the first patients to join her practice was E.S. E.S. was one of Dr C.I.'s favourite patients. As a retired nurse turned active grandmother, E.S. spent most of her time spoiling her grandchildren.

One morning, E.S. booked a same-day appointment for new-onset left-sided weakness. Thinking that she could have been having a stroke, Dr C.I. sent E.S. by EMS to a nearby hospital. Unfortunately, her computed tomography (CT) scan showed a new diagnosis of glioblastoma multiforme with significant vasogenic oedema. She was given a prescription for dexamethasone and sent home for follow-up with oncology and neurosurgery.

The next week, E.S. was seen by medical oncology, neurosurgery, and radiation oncology in a multidisciplinary clinic. When she found out there were no options for curative intervention, E.S. elected to pursue a palliative approach to her care. Her oncologist referred her to the outpatient palliative care clinic.

Dr C.I. was saddened by E.S.'s diagnosis and prognosis. She booked a supportive visit to see E.S. and her family. They spent some time discussing E.S.'s options and reviewed E.S.'s symptoms, as well as her life and accomplishments.

Over time, E.S.'s symptoms became more complex and required increasing support of the palliative care team. In her last days of life, her symptoms were deemed refractory to all usual interventions and E.S. and her family elected to pursue palliative sedation, with the support of Dr C.I. and the palliative care team (see Chapter 20 on palliative sedation).

The next day, Dr C.I. had a busy clinic. Her electronic medical record broke down and she had some last-minute bookings. She did not have a chance to think about E.S. until her drive home. In the car, Dr C.I. was overwhelmed with a wave of sadness and started to cry. She would miss E.S.

Question 7. How can Dr C.I. cope with the loss of E.S.?

Healthcare professionals often forge strong relationships with the patients with whom they work. In Dr C.I.'s case, her relationship with E.S. spanned over three decades. It is not surprising therefore that healthcare providers can feel a sense of grief when a patient dies. The process of grieving patient death is different from traditional bereavement due to a healthcare provider's work context and culture.[30,31] Literature suggests that there is a 'hidden curriculum' in physician training that encourages a repression of emotional reactions.[30,31] As a result, many healthcare providers avoid

outward displays of emotion for fear of being seen as incompetent or unable to cope. This leads to grief that is not openly acknowledged and socially supported, a process known as disenfranchised grief.[32]

Grieving patient loss is further complicated by healthcare providers' own professional roles and expectations. Many healthcare providers feel they need to set aside emotional reactions to distance themselves from the loss and remain focused on the technical aspects of their roles.[33] In Dr C.I.'s case, she delayed her emotional response to E.S.'s death until her work for the day was complete. A professional grieving model has been proposed that describes this fluctuation between repressing and experiencing grief reactions.[34] In the 'dual process model' of bereavement, there is an oscillation between orienting either towards the loss experience or away from the loss towards continued engagement with life, [13] or, in the case of healthcare professionals, grieving and avoiding the grief experience in order to 'get the job done'.[34]

Failing to openly acknowledge loss in the workplace can lead to job-related burnout.[31] Healthcare providers' responses to patient loss are highly individualized but should be recognized, normalized, and validated. Dr C.I. might find it helpful to seek respite from her clinical demands and spend time focusing on activities that she enjoyed. Rituals to acknowledge the patient and allow the care team to feel openly supported in their grief can also help to develop closure.

Case 14.4 (continued)

Dr C.I. was not on call and spent her weekend doing things that she enjoyed: biking, cooking, and doing yoga. On Monday, she received the announcement of E.S.'s death. Dr C.I. took some time to write E.S.'s family a note about what their relationship had meant to her and shared her experience with her colleagues. Several months later, her clinic held a memorial service with the staff and other physicians to acknowledge the patients who had died that year. They read each of the patients' names and said a word or two to remember them. Dr C.I. spoke about her deceased patients, including E.S.

References

1. **Strobe M**, **Schut H**, **Stroebe W** (2007) Health outcomes of bereavement. *Lancet*, **370**, 1960–73.
2. **Elwert F**, **Christakis N.** The effect of widowhood on mortality by the causes of death of both spouses. *Am J Public Health*, **98**, 2092–8. doi:10.2105/AJPH.2007.114348
3. **Sung S**, **Dryman T**, **Marks E** *et al.* (2011) Complicated grief among individuals with major depression: prevalence, comorbidity, and associated features. *J Affect Disord*, **134**, 453–8. doi.org/10.1016/j.jad.2011.05.017
4. **Shear K**, **Simon N**, **Wall M** *et al.* (2011) Complicated grief and related bereavement issues for DSM-5. *Depress Anxiety*, **28**(2), 103–17.
5. **Ringdal G**, **Jordhoy M**, **Ringdal K** *et al.* (2001) The first year of grief and bereavement in close family members to individuals who have died of cancer. *Palliat Med*, **15**, 91–105.
6. **Casarett D**, **Kutner J**, **Abrahm J** (2001) Life after death: a practical approach to grief and bereavement. *Ann Intern Med*, **134**(3), 208–15.
7. **Pereira J** (2016) *The Pallium Palliative Pocketbook*, 2nd edn. Pallium Canada, Ottawa, ON.
8. **Bowlby J** (1961) Processes of mourning. *Int J Psycho-Anal*, **42**, 317–40.
9. **Maciejewski P**, **Zhang B**, **Block S** *et al.* (2007) An empirical examination of the stage theory of grief. *JAMA*, **297**, 716–23.
10. **Kübler-Ross E** (1969) *On Death and Dying*. Macmillan, New York, NY.

11. **Hall C** (2014) Bereavement theory: recent developments in our understanding of grief and bereavement. *Breave Care*, **33**, 7–12. doi:10.1080/02682621.2014.902610
12. **Worden J** (2008) *Grief Counseling and Grief Therapy: A Handbook for the Mental Health Practitioner*, 4th edn. Springer, New York, NY.
13. **Stroebe M**, **Schut H** (2010) The dual process model of coping with bereavement: a decade on. *OMEGA*, **61**(4), 273–89.
14. Stroebe M, Schut H. (1999). The dual process model of coping with bereavement: Rationale and description. *Death Stud*, **23**(3), 197–224. doi:10.1080/074811899201046. PMID: 10848151.
15. **Forte A**, **Hill M**, **Pazdar R** *et al.* (2004)Bereavement care interventions: a systematic review. *BMC Palliat Care*, **3**, 3. doi:10.1186/1472-684X-3-3
16. **Theut S**, **Jordan L**, **Ross L** *et al.* (1991) Caregiver's anticipatory grief in dementia: A pilot study. *Int J Aging Hum Dev*, **33**(2), 113–18.
17. **Holley C**, **Mast B** (2009) The impact of anticipatory grief on caregiver burden in dementia caregivers. *Gerontologist*, **49**(3), 388–96. doi:10.1093/geront/gnp061
18. **Kersting A**, **Brahler E**, **Glaesmer H** *et al.* (2001) Prevalence of complicated grief in a representative population-based sample. *J Affect Disord*, **131**, 339–43. doi:10.1016/j.jad.2010.11.032
19. **Nielsen M**, **Neergaard M**, **Jensen A** *et al.* (2017) Predictors of complicated grief and depression in bereaved caregivers: a nationwide prospective cohort study. *J Pain Symptom Manage*, **53**(3), 540–50.
20. **Newson R**, **Boelen P**, **Hek K** *et al.* (2011) The prevalence and characteristics of complicated grief in older adults. *J Affect Disord*, **132**, 231–8. doi:10.1016/j.jad.2011.02.021
21. **Sheldon F** (1998) Bereavement. *BMJ*, **316**, 456–8.
22. **American Psychiatric Association** (2013) *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, 5th edn. American Psychiatric Publishing, Arlington, VA.
23. **Conwell Y**, **Van Orden K**, **Caine E** (2011) Suicide in older adults. *Psychiatr Clin North Am*, **34**(2), 451–68. doi:10.1016/j.psc.2011.02.002
24. **Stroebe M**, **Strobe W**, **Abakoumkin G** (2005) The broken heart: suicidal ideation in bereavement. *Am J Psychiatry*, **162**, 2178–80.
25. **Heisel M**, **Flett G** (2006) The development and initial validation of the geriatric suicide ideation scale. *Am J Geriatr Psychiatry*, **14**, 742–51.
26. **Warden S**, **Spiwak R**, **Sareen J** *et al.* (2014) The SAD PERSONS scale for suicide risk assessment: a systematic review. *Arch Suicide Res*, **18**(4), 313–26. doi:10.1080/13811118.2013.824829
27. **Kennedy S**, **Lam R**, **McIntyre R** *et al.* (2016) Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. *Can J Psychiatry*, **61**, 540–60. doi:10.1177/0706743716659417
28. **Shear K**, **Frank E**, **Houck P** *et al.* (2005) The treatment of complicated grief. *JAMA*, **293**, 2601–8.
29. **Kissane D**, **McKenzie M**, **Bloch S** *et al.* (2006) Family focused grief therapy: a randomized, controlled trial in palliative care and bereavement. *Am J Psychiatry*, **163**, 1208–18.
30. **Sansone R**, **Sansone L** (2012) Physician grief with patient death. *Innov Clin Neurosci*, **9**(4), 22–6.
31. **Redinbaugh E**, **Sullivan A**, **Block S** *et al.* (2003) Doctors' emotional reactions to recent death of a patient: cross sectional study of hospital doctors. *BMJ*, **37**, 185–91.
32. **Doka K** (1999) Disenfranchised grief. *Bereavement Care*, **18**, 37–9. doi:10.1080/02682629908657467
33. **Whitehead P** (2014) The lived experience of physicians dealing with patient death. *BMJ Support Palliat Care*, **4**, 271–6. doi:10.1136/bmjspcare-2012-000326
34. **Papadatou D** (2000) A proposed model of health professionals' grieving process. *Omega*, **4**(1), 59–77.

Chapter 15

Wounds in advanced illness

Cheryl Hurley and Vincent Maida

'*Treat the whole patient not just the hole in the patient.*'

(Dr R. Gary Sibbald 2000)[1]

Attitude

To enable each learner to:

- Exemplify a 'whole patient' approach.
- Realize the importance of interprofessional collaboration.
- Consider that suffering from wounds goes beyond physical symptoms and may include psychological, social, existential, spiritual, and functional dimensions.
- Plan strategies that promote prevention.
- Reflect on the multiple successful endpoints in wound management: wound healing, wound stabilization (maintenance), wound palliation, and the fulfilment of patient-centred concerns.

Skills

To enable each learner to:

- Demonstrate proficiency in setting realistic goals.
- Measure and record pain and polysymptom distress generated by wounds.
- Diagnose and treat superficial and deep wound infections.
- Integrate local and systemic treatment modalities.
- Write appropriate orders that project strategies for the prevention of wounds.

Knowledge

To enable each learner to:

- Cite and describe the multiple wound classes and wound types, along with their aetiologies and risk factors.
- Compare and contrast the multiple assessment systems for pressure ulcers and malignant wounds.

[1] Reproduced with permission from Sibbald RG, et al. 'Preparing the wound bed-debridement, bacterial balance, and moisture balance'. Ostomy Wound Manage. Vol. 46 Issue 11, pp.14–22, 24–8, 30–5; Copyright © 2000 HMP publications.

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- Employ the presence or absence of wounds as a prognostic factor.
- Differentiate between healable and non-healable wounds.
- Utilize the 'DIME' paradigm to assess and guide treatment for potential wound healing.
- Evaluate the success of treatment plans through the measurement of objective parameters.

Case 15.1

A.D. is a 95-year-old demented gentleman from a nursing home who was admitted to hospital with 'failure to thrive'. He is completely dysphagic. Examination reveals a necrotic stage IV pressure ulcer, measuring 8 cm in diameter and involving his sacral area, and bilateral unstageable pressure ulcers, each measuring 4 cm in diameter, of both heels. Dr P.M. counsels the daughter about the natural history of advanced dementia and explains the prognostic implications of pressure ulcers and other wounds. The daughter elects for a palliative approach. Dr P.M. orders intravenous (IV) metronidazole to help combat the malodour associated with the pressure ulcer.

Question 1. What is the magnitude of wound-related issues in the palliative care setting?

Patients with advanced illness, cancer and non-cancer, have a high prevalence and incidence of wounds that rank among the highest levels of all sectors/cohorts within healthcare.[1] More than 60% of patients referred for palliative care have at least one wound at referral.[1] The most common wound class occurring in cancer and non-cancer patients are pressure ulcers, with a prevalence of 22.4%.[1] The most common anatomic site for wounds in patients with advanced illness is the sacrum/coccyx area.[1,2] Cancer patients have high prevalence and incidence of malignant wounds, ostomies, and traumatic wounds, and have a propensity for wounds involving their abdomen and chest/breast areas.[1] Non-cancer patients have high prevalence and incidence of traumatic wounds, ostomies, and venous leg ulcers, and have a propensity for wounds involving their extremities.[1]

Question 2. What are costs of wounds?

As a human cost, wounds are a leading source of suffering and reduced quality of life.[3,4,5] They commonly cause physical symptoms such as pain, exudation, odour, pruritus, bleeding, and disfigurement. As the wound progresses, the time intensity of wound care, the repulsive nature of the wound, and the shame and embarrassment experienced by the patient all contribute to significant secondary social, psychological, and spiritual/existential suffering.[3,4,5,6] Moreover, they may be associated with reduced survival.[7] In addition, recent qualitative research has shown that wounds may cause significant indirect costs through the burden and stress they cause family members, caregivers, and healthcare professionals.[3] As a resource cost, it is estimated that the United States spends more than $50 billion annually on the management of chronic wounds.[8] Unfortunately, very little is spent on wound prevention.

Question 3. What constitutes successful wound management?

Wound management[3,9] is an overarching term that encompasses multiple goals, including wound healing, wound maintenance (stabilization), and wound palliation[10] (see Figure 15.1). However, patients with advanced illnesses often have multiple incurable systemic, iatrogenic, and comorbid

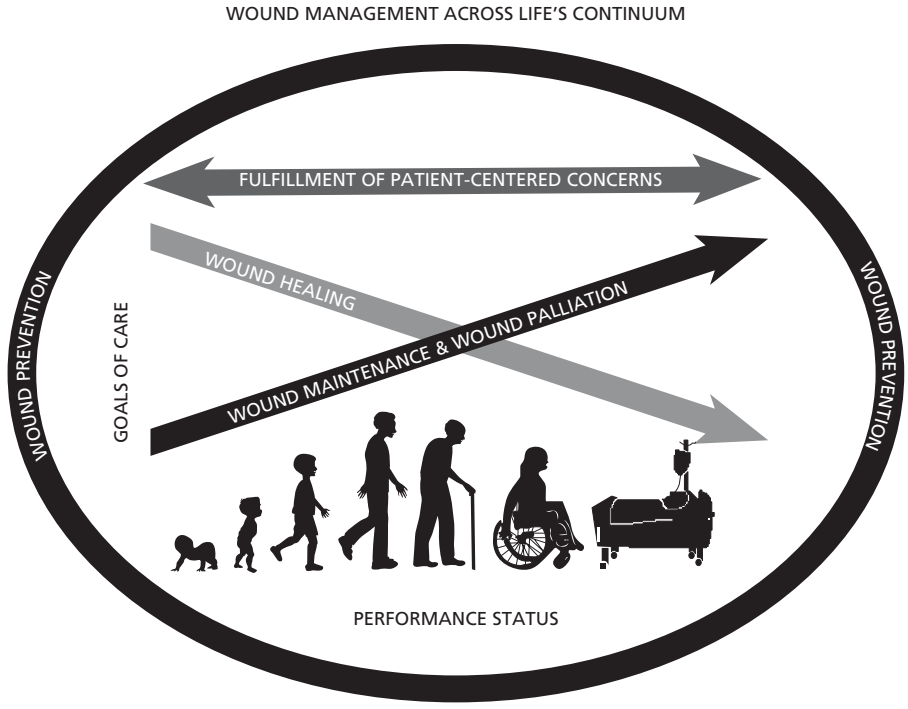


Fig. 15.1 A new paradigm for wound management.
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factors mitigating against healing[9] and life expectancies often not long enough to permit healing. The inability to heal a wound is not a failure if other goals can be achieved. As patients with existing wounds are at risk of developing additional wounds, the pinnacle of success would be wound prevention. Also important is the prevention of wound-related complications. Certain diagnostic measurements, including histopathology, ultrasonography, laser Doppler flowmetry, and magnetic resonance imaging (MRI), may be considered for chronic wounds poorly responding to treatment.[11] However, goals of care may change as the natural history of disease unfolds, and they are not mutually exclusive as wound healing may lead to wound palliation, and vice versa.[12] Ultimately, successful wound management is predicated on a patient-centred approach, maximizing comfort, dignity, and quality of life.

Question 4. What are the risk factors for pressure ulcer development?

A pressure ulcer is an ischaemic necrosis of skin and underlying tissues resulting from arterial, venous, and lymphatic stasis.[13] Although prolonged, unrelieved pressure is the dominant mechanical factor, repetitive shearing and friction forces are also contributory.[13] Pressure ulcers generally develop over bony protuberances.[13] Patient-related risk factors include advanced age, high comorbid disease burden, cachexia, neuropathy, paralysis, and peripheral vascular disease.[13] Although numerous risk assessment tools exist for pressure ulcers, the Braden Scale has the greatest acceptance.[14] A striking correlation between the Braden Scale and the Palliative Performance Scale (PPS) in patients with advanced cancer and non-cancer illness supports the

use of PPS, as a proxy, for the assessment of pressure ulcer development risk in this clinical context.[15]

The nursing home is advised of A.D.'s risk of pressure ulcer development and creates a care plan to prevent further ulcers that is in keeping with his goals of care.

Question 5. How are pressure ulcers classified?

The two classification systems that are most commonly used are those forwarded by the National Pressure Injury Advisory Panel (NPIAP)[16] and the European Pressure Ulcer Advisory Panel (EPUAP).[17] The International NPIAP/EPUAP Classification System describes six grades of pressure injuries.[18] However, pressure ulcers are usually complex and may contain components of multiple stages/grades. Moisture lesions, also termed 'incontinence dermatitis' or 'incontinence-associated dermatitis', should be differentiated from pressure ulcers.[19] Moisture lesions manifest as blanchable erythema, unlike the non-blanchable erythema seen in stage I pressure ulcers, and tend to occur where there is intertriginous skin contact.[19] Histopathogically, moisture lesions demonstrate inflammation, in contrast to the ischaemia seen with pressure ulcers.[19]

Question 6. What is the DIME paradigm for wound healing?

Sibbald *et al.* have developed a paradigm to guide potential wound healing, based on the wound bed preparation model and enabled by the mnemonic acronym '*DIME*'.[20,21] The four elements of DIME are not mutually exclusive and attaining one may facilitate achieving others.

D = Debridement and downloading

Necrotic and non-viable tissue overlying and/or within a wound bed must be debrided to promote healing.[20,21] Some wound products (see Table 15.1) may carry out a limited amount of autolytic debridement[20] and there has been interest in employing topical enzymatic (collagenase or papain) and larval (maggot) therapy for debridement purposes.[20,21] Other options include sharp debridement at the bedside, or surgical debridement in the operating room when the wound is large and/or when analgesia and haemostasis cannot be achieved at the bedside.

Pressure redistribution[21] is an important part of treating and preventing wounds, including pressure ulcers, neurotropic diabetic foot ulcers, and arterial foot ulcers. As patients become increasingly bed-bound, this may be achieved through strategies that afford pressure relief and increase overall contact area[21] (see Figure 15.2) and should also take into account factors that affect the micro-climate of the wound, namely heat and moisture retention.[21,22]

I = Infection and inflammation

While acute wounds tend to be contaminated or colonized with Gram-positive organisms, chronic wounds usually harbour Gram-negative and anaerobic organisms.[20] Wound colonization involves a state of 'bacterial balance' where organisms may be replicating, but they are held in check by host resistance factors.[20] With a state of 'bacterial imbalance', replicating organisms overrun host resistance factors, which leads to superficial compartment infection (critical colonization), deep compartment infection, and systemic infection (sepsis).[20] Consequences include abscesses, sinuses, fistulae, compartment syndrome, and osteomyelitis. Pain escalation is a reliable indicator for the presence of infection and should always prompt clinicians to rule out such complications. Superficial compartment infections are optimally treated with topical antimicrobial dressings (see Table 15.1).[20] Deep compartment infections and systemic infections require systemic antibiotic therapies, as per published guidelines and validation by culture and sensitivity assays.[20]

Table 15.1 Common local wound management products

Wound product Primary objective	Product category	Sample product	Collateral benefits
Absorbent	Hydrofibre	Aquacel® Ag	Topical antimicrobial
Absorbent	Alginate	Katostat™	Topical haemostatic
Absorbent	Alginate with ethylene methylacrylate contact layer	Silvercel™ non-adherent	Topical antimicrobial Non-adherent
Absorbent	Cellulose pulp with polypropylene contact layer	Mesorb®	Non-adherent + protects clothing
Absorbent	Textile with silver complex	InterDry™ Ag	Skinfold management to treat and prevent moisture lesions
Hydrating agent	Hydrocolloid	NU-DERM™ Hydrocolloid	Autolytic debridement
Hydrating agent	Hydrogel	Purilon™ Gel	Autolytic debridement
Protease modulator	ORC/collagen	Promogran™	Topical haemostatic
Protease modulator	ORC/collagen	Prisma™	Topical antimicrobial Topical haemostatic
Topical antimicrobial	Nanocrystalline silver	Acticoat™	Absorbent
Topical antimicrobial	Ionic silver + hydrogel	Silvasorb® Gel	Hydrating agent + topical antimicrobial
Topical antimicrobial	Cadexomer iodine	Iodosorb™	Absorbent
Topical antimicrobial	10% povidone iodine	Inadine™	Non-adherent
Topical antimicrobial	Honey	Medihoney®	Hydrating agent + debridement
Anti-odour	Metronidazole	Metrogel™	Topical antimicrobial
Anti-odour	Charcoal	Actisorb™ Silver 220	Absorbent
Non-adherent wound contact layer	Cotton + polyethylene contact layer	Telfa™	Allows moisture vapour exchange
Non-adherent wound contact layer	Polyamide net covered with silicone	Mepetel®	Flexible and conforms to contours
Protect periwound skin	Barrier cream	Cavilon™	Hypoallergenic

M = Moisture balance

Although 'moist wound healing'[23] applies to most healable wounds, moisture imbalance at either extreme may be equally deleterious to wounds. Wound exudates are rich in matrix metalloproteinases, bacterial toxins, pro-inflammatory mediators, and products of tissue necrosis.[20] Excess wound exudate promotes maceration of the wound bed and periwound tissues, reducing tissue tensile strength and creating ideal proliferating conditions favouring many microorganisms.[20] In choosing an absorptive dressing, healthcare professionals should consider wound

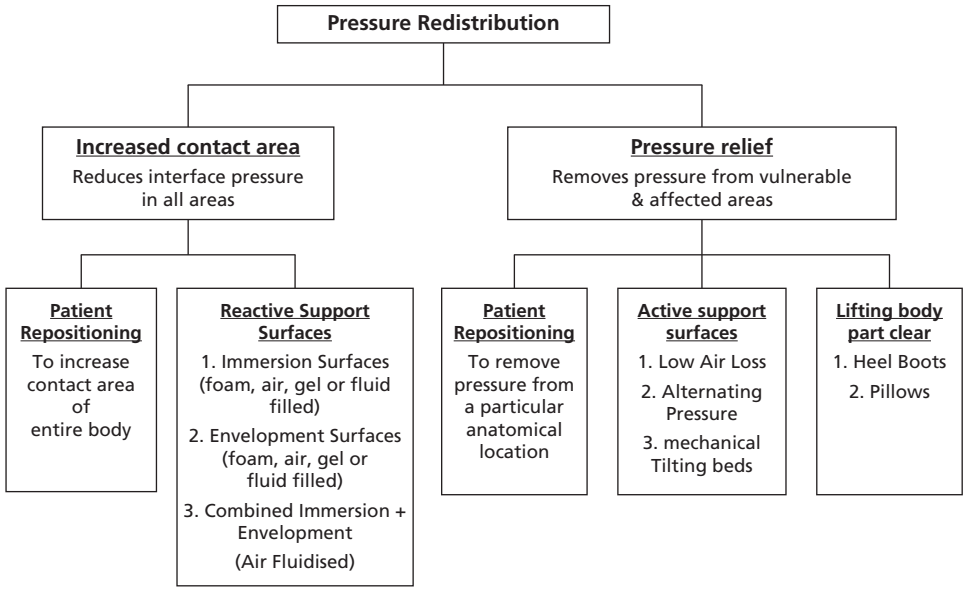


Fig. 15.2 Components of pressure redistribution.
Adapted with permission from 'International review. Pressure ulcer prevention: pressure, shear, friction and microclimate in context. A consensus document'. London. *Wounds International,* 2010. Available from http://www.woundsinternational.com/pdf/content_8925.pdf

morphology, patient-centred concerns, convenience, availability, and economy. Generically, the absorptive capacity of interactive dressings, in descending order, is as follows: foams > hydrofibres > alginates > hydrocolloids. Absorptive padding may be used as primary or secondary dressings where exudation is high.[26] In wounds where exudation is extreme, negative pressure wound therapy (NPWT) may be considered.[20,21] 'Moist wound healing' is not appropriate for non-healable wounds, including malignant wounds or gangrene. In such cases, cleansing and/or painting with antiseptics with low toxicity is favoured.[20]

E = Edge effects

Despite attending to the *D*, *I*, and *M* elements of the above paradigm, wound healing may still be stalled, as evidenced by failure of the dermis and/or epithelium to 'edge' inwards.[24] In such cases, NPWT, hyperbaric oxygen therapy (HBOT), growth factor therapy, and skin grafting[24] may be considered for patients with a sufficient prognosis to potentially benefit.

Question 7. What are some clinical paradigms for diagnosing wound infection?

Sibbald *et al*. have developed enablers to facilitate the clinical diagnosis of infection through the use of the following mnemonic acronyms: '*NERDS*' for superficial compartment infections, and '*STONES*' for deep compartment infection.[20]

- *NERDS*:

N = Non-healing or deterioration

E = Exudate ↑

R = Red wound bed (hypergranulation)

D = Debris in wound

S = Smell ↑

- *STONES*:

S = Size of wound ↑

T = Temperature ↑ (quantified using infrared thermometry)

O = Os (palpable exposed bone)

N = New areas of breakdown

E = Exudate ↑, Erythema, oEdema

S = Smell ↑

Three or more *NERDS* criteria is highly sensitive and specific for the presence of superficial compartment infection, while four or more of the *STONES* criteria is highly sensitive and specific for deep compartment infection.[20] In addition to the *NERDS/STONES* criteria, pain escalation is also a very robust predictive factor for the presence of infection.[28]

Case 15.2

S.D., 55, presents after neglecting a right breast mass for over a year. S.D. has a significant anxiety disorder. S.D. has a large exophytic wound involving her entire right breast, measuring approximately 12 cm x 12 cm, with a central cavitation measuring 2 cm x 3 cm and approximately 1 cm deep. The fungating wound is surrounded by a 4 cm-wide corona of erythematous induration, with multiple scattered 1–2 cm-wide subcutaneous nodules that are beginning to spread laterally. The ulcerated centre oozes blood and the surrounding fungating tissue has patches of purulent exudate. She is promptly referred to oncology; systemic chemotherapy is initiated and palliative care is consulted for symptom management. S.D. reports having '10/10' pain, associated with dressing changes. She experiences shame and embarrassment due to the wound's foul odour, which nauseates her and interferes with her appetite. S.D. also has '7/10' anxiety due to the fear of bleeding through her clothing.

Question 8. How common are malignant wounds? How are malignant wounds classified?

Malignant wounds, manifestations of primary skin neoplasms, their local recurrences, or metastatic deposits from a remote primary site, occur in up to 15% of advanced cancer patients.[1] Malignant wounds are heterogeneous and complex, usually containing multiple morphologic features, the most common feature being fungating/exophytic morphology, occurring in 60% of malignant wounds.[1]

Question 9. What tools are available to assess malignant wounds?

The Toronto Symptom Assessment System for Wounds (TSAS-W)[4] was modelled after the Edmonton Symptom Assessment System (ESAS) and is a method to objectively quantify the pain and polysymptom burden caused by wounds of all classes. Summation of all applicable TSAS-W parameters (11-point numeric rating scales) equates to the Global Wound Distress Score (GWDS).[4]

Question 10. What disease-modulating therapies are effective in treating malignant wounds?

Potential disease-modulating therapies for malignant wounds include systemic chemotherapies, hormonal therapies, radiation therapy, photodynamic therapy, and electrochemotherapy.[25,26,27] Therefore, all patients with malignant wounds warrant consultations with medical and radiation oncologists. Surgical consultation may also be considered for bulky tumours to aid in symptom management, as traditional chemoradiation may cause the wound to enlarge and become more problematic. As a topical treatment option, a Cochrane systematic review supports the use of topical 6% miltefosine, a cytotoxic agent, as a method to reduce progression of fungating wounds.[28]

Question 11. What is the role of the interprofessional team in the management of malignant wounds?

Important insights have been gained on the 'lived experience' of having a malignant wound,[6] illustrating the importance of consulting social workers, psychologists, and spiritual advisors to help manage a patient's psychosocial, spiritual, and existential suffering. Occupational therapists may assess self-care needs to ensure that the patient's environment is functional and safe and to make recommendations regarding assistive devices and clothing options. Physiotherapists may provide valuable assistance in the prevention and treatment of complications such as reflex sympathetic dystrophies, oedema, and lymphoedema. Physiotherapists may also be involved in a number of emerging complementary wound therapies such as ultrasound, laser, and electromagnetic therapy.

Question 12. What are the available methods to treat the most common wound-related symptoms?

Pain

Pain is the most common symptom associated with malignant wounds, occurring in almost one-third of patients.[4] Removing adherent dressing materials, wound cleansing, wound debridement, and application of new dressing materials may all evoke pain.[28] Optimal pain management requires a combination of systemic and local analgesics, while striving to employ strategies to prevent pain.[29,30,31] Wound-related pain is due to both inflammatory and neuropathic mechanisms, requiring the use of systemic opioids and adjuvant analgesics.[30] Whenever possible, systemic analgesics should be used with promising local analgesic strategies.[31] Unfortunately, the efficacy of topical morphine remains questionable, with only three of eight randomized controlled trials demonstrating analgesic efficacy.[32,33] Opioid-induced inhibition of wound healing is also an emerging concern.[34] A recent interest in the potential role of topical medical cannabis-based medicines for wound-related pain has yielded promising case reports.[35,36] Optimally, rapid-onset/short-acting opioids from the fentanyl family should be employed to prevent incident pain associated with dressing changes.[29] However, there has been recent interest in the role of lidocaine and ketamine for wound-related pain.[30,37,38] Non-adherent contact layer dressings (see Table 15.1)[25] may also prevent pain during dressing changes.

Case 15.2 (continued)

S.D.'s wound-related pain is managed with the combination of a regularly scheduled oral opioid, an adjuvant for neuropathic pain, and subcutaneous fentanyl for wound care.

S.D. is prescribed fentanyl for dressing changes.

Exudate

Exudation is the second most reported symptom, occurring in just under one-third of patients,[4] resulting from the secretion of vascular permeability factor by cancer cells,[40] causing high capillary permeability within wound tissue. Increased hydrostatic pressure from venous and lymphatic obstruction also may be contributory. The inappropriate use of hydrating agents (hydrogels and hydrocolloids) may increase exudation. Periwound skin must be protected, as wound exudate promotes maceration and potential skin toxicity. Protection may be achieved by the application of hydrocolloids or a barrier product (see Table 15.1). The choice should be individualized and based on patient-centred concerns, product availability, convenience, and economics. Extreme wound and/or fistulous effluent may warrant consultation from an enterostomal nurse specialist to guide the application of ostomy pouches. Although NPWT is usually contraindicated for malignant wounds, due to concern of encouraging tumour growth, a case series of patients with short survival prognoses did report successful management of highly exudative, malodorous wounds via NPWT.[39]

Odour

Although odour is reported by only about 10% of patients, it is one of the main concerns identified by affected patients.[4,6] It is mainly generated by the presence of decomposing necrotic tissue and Gram-negative infections.[40] A recent study suggested systemic maintenance doses of metronidazole was better for odour when dealing with bulky or deep-seated tumours.[42] However, systemic use of metronidazole is limited by side-effects, including nausea, metallic taste, and a disulfiram-like reaction when used in conjunction with alcohol.[40] A systematic review of topical treatments to control the odour of malignant fungating wounds gave both topical metronidazole (0.75% gel or 1.0% solution) and charcoal-containing dressings a B grade recommendation.[41] Other interventions include wound cleansing, painting with antiseptics, and careful debridement of clearly necrotic tissue. Aromatherapy oils, baking soda, and pet litter may also provide further control of wound-related odours.[28]

Bleeding

Although it occurs in less than 10% of patients,[4] bleeding from a malignant wound is a potentially traumatic event. Bleeding may occur spontaneously or may be incited by dressing changes.[28] Minor bleeding may be managed locally with calcium alginates, oxidized regenerated cellulose (ORC)/collagen, topical thromboplastin (100 U/ml), and silver nitrate cautery.[28] A Cochrane review found topical tranexamic acid reduced bleeding in cardiac, orthopaedic, and otolaryngologic surgeries.[43] However, its use in wound management is limited to case reports. Moderate to severe cases require consideration of local vessel ligation, electrocautery, cryotherapy, arterial embolization, or a trial of antifibrinolytic agents. As patients are approaching end of life, one should consider discontinuing all anticoagulants.

Case 15.2 (continued)

Further management of S.D.'s wound includes daily dressing changes to control odour and bleeding. Topical metronidazole is applied to the areas of purulent exudate, with improved odour control. Adherent dressing materials are avoided and haemostatic dressings are applied to minimize bleeding.

Question 13. What are the prognostic implications of wounds in patients with advanced illness?

Pressure ulcers are increasingly being regarded as markers for limited survival, as opposed to direct causes of mortality.[7] Survival of patients with malignant wounds has significantly improved over the past four decades. The average life expectancy has improved from 3 months after the development of a malignant wound[44] to a survival of 11.27 months.[45] The presence of a malignant wound in patients with higher levels of performance status should not be regarded as a disqualifying criterion for continued oncologic therapies.

Summary

Patients with advanced illness have a high prevalence and incidence of wounds from multiple wound classes. Wounds represent a major source of suffering and reduced quality of life, owing to their multidimensional nature. They are also an increasing concern from a healthcare economic standpoint. Given that wounds are, metaphorically, 'windows into the health of the patient', they may be used as prognostic factors, with the potential to enhance the acumen of currently available prognostic instruments and models. Successful wound management is predicated upon realistic goal setting, in conjunction with wound prevention strategies.

References

1. **Maida V**, **Corbo M**, **Irani S** *et al.* (2008) Wounds in advanced illness: a prevalence and incidence study based on a prospective case series. *Int Wound J*, **5**(2), 305–14.
2. **Artico M**, **Dante A**, **D'Angelo D** *et al.* (2018) Prevalence, incidence and associated factors of pressure ulcers in home palliative care patients: a retrospective chart review. *Palliat Med*, **32**(1), 299–307.
3. **Chrisman CA** (2010) Care of chronic wounds in palliative care and end-of-life patients. *Int Wound J*, **7**(4), 214–35.
4. **Maida V**, **Ennis M**, **Kuziemsky C** (2009) The Toronto Symptom Assessment System for Wounds (TSAS-W): a new clinical and research tool. *Adv Skin Wound Care*, **22**(10), 468–74.
5. **Schulz V**, **Kozell K**, **Biondo PD** *et al.* (2009) The malignant wound assessment tool: a validation study using a Delphi approach. *Palliat Med*, **23**(3), 266–73.
6. **Alexander S** (2013) Time to get serious about assessing—and managing psychosocial issues associated with chronic wounds. *Curr Opin Support Palliat Care*, **7**(1), 95–100.
7. **Maida V**, **Ennis M**, **Kuziemsky C**, **Corban J** (2010) Wounds and survival in noncancer patients. *J Palliat Med*, **13**(4), 453–9.
8. **Fife CE**, **Carter MJ**, **Walker D**, **Thomson B** (2012) Wound care outcomes and associated cost among patients treated in US outpatient wound centers: data from the US Wound Registry. *Wounds*, **24**(1), 10–17.
9. **Maida V** (2013) Wound management in patients with advanced illness. *Curr Opin Palliat Care*, **7**(1), 73–9.

10. **Ferris FD**, **Al Khateib AA**, **Fromantin I** *et al*. (2007) Palliative wound care: managing chronic wounds across life's continuum: a consensus statement from the International Palliative Wound Care Initiative. *J Palliat Med*, **10**(1), 37–9.
11. **Romanelli M**, **Miteva M**, **Romanelli P**, **Barbanera S**, **Dini V** (2013) Use of diagnostics in wound management. *Curr Opin Support Palliat Care*, **7**(1), 106–10.
12. **Liao S**, **Arnold RM** (2007) Wound care in advanced illness: application of palliative care principles. *J Palliat Med*, **10**(5), 1159–60.
13. **Grey JE**, **Enoch S**, **Harding K** (2006) ABC of wound healing: pressure ulcers. *BMJ*, **332**, 472–5.
14. **Pancorbo PL**, **Garcia-Fernandez FP**, **Lopez-Medina IM** *et al*. (2006) Risk assessment scales for pressure ulcer prevention: a systematic review. *J Adv Nurs*, **54**(1), 94–110.
15. **Maida V**, **Lau F**, **Downing M**, **Yang J** (2008) Correlation between Braden Scale and Palliative Performance Scale in advanced illness. *Int Wound J*, **5**(4), 585–90.
16. **National Pressure Injury Advisory Panel (NPIAP).** http://www.npiap.com
17. **European Pressure Ulcer Advisory Panel (EPUAP).** http://www.epuap.org
18. **National Pressure Injury Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance**. (2019) *Prevention and Treatment of Pressure Ulcers/Injuries: Quick Reference Guide*2019. internationalguideline.com/static/pdfs/Quick_Reference_Guide-10Mar2019.pdfcontent/uploads/2016/10/quick-reference-guide-digital-npuap-epuap-pppia-jan2016.pdf
19. **Defloor T**, **Schoonhaven L**, **Fletcher J**, *et al*. (2005) Statement of the European Pressure Ulcer Advisory Panel-Pressure Ulcer Classification: differentiation between pressure ulcers and moisture lesions. *J Wound Ostomy Continence Nurs*, **32**(5), 302–6.
20. **Sibbald RG**, **Woo K**, **Ayello EA** (2006) Increased bacterial burden and infection: the story of NERDS and STONES. *Adv Skin Wound Care*, **19**(8), 447–61.
21. **Wounds International** (2010) *Pressure ulcer prevention: pressure, shear, friction and microclimate in context. A consensus document*. Wounds International, London. http://www.woundsinternational.com/pdf/content_8925.pdf
22. **White-Chu E**, **Reddy M** (2013) Pressure ulcer prevention in patients with advanced illness. *Curr Opin Support Palliat Care*, **7**(1), 111–15.
23. **Winter GD**, **Scales JT** (1963) Effect of air drying and dressings on the surface of the wound. *Nature*, **197**, 91–2.
24. **Woo K**, **Ayello EA**, **Sibbald RG** (2007) The edge effect: current therapeutic options to advance the wound edge. *Adv Skin Wound Care*, **20**, 99–117.
25. **Woo KY**, **Sibbald RG** (2010) Local wound care for malignant and palliative wounds. *Adv Skin Wound Care*, **23**, 417–28.
26. **Vempati P**, **Knoll M**, **Dharmarajan K**, **Green S**, **Tierstein A**, **Bakst R** (2016) Palliation of ulcerative breast lesions with radiation. *Anticancer Res*, **36**(9), 4701–6.
27. **Grocotte P**, **Gethin G**, **Probst S** (2013) Malignant wound management in advanced illness: new insights. *Curr Opin Support Palliat Care*, **7**(1), 101–5.
28. **Adderley U**, **Smith R** (2007) Topical agents and dressings for fungating wounds. *Cochrane Database Syst Rev*, **2**, CD003948.
29. **Gallagher R** (2013) The management of wound-related procedural pain (volitional pain) in advanced illness. *Curr Opin Support Palliat Care*, **7**(1), 80–5.
30. **Woo K**, **Abbott L**, **Librach L** (2013) Evidence-based approach to manage persistent wound-related pain. *Curr Opin Support Palliat Care*, **7**(1), 86–94.
31. **Gallagher RE**, **Arndt DR**, **Hunt KL** (2005) Analgesic effects of topical methadone: a report of four cases. *Clin J Pain*, **21**(2), 190–2.
32. **Zaslansky R**, **Ben-Nun O**, **Ben-Shitrit S**, **Ullmann Y**, **Kopf A**, **Stein C** (2014) A randomized, controlled, clinical pilot study assessing the analgesic effect of morphine applied topically onto split-thickness skin wounds. *J Pharm Pharmacol*, **466**(11), 1559–66.

33. **Graham T**, **Grocott P**, **Probst S**, **Wanklyn S**, **Dawson J**, **Gethin G** (2013) How are topical opioids used to manage painful cutaneous lesions in palliative care? A critical review. *Pain*, **154**(10), 1920–8.
34. **Farley P** (2011) Should topical opioid analgesics be regarded as effective and safe when applied to chronic cutaneous lesions? *J Pharm Pharmacol*, **63**(6), 747–56.
35. **Maida V** (2017) Medical cannabis in the palliation of malignant wounds—a case report. *J Pain Symptom Manage*, **53**(1), e4–6.
36. **Maida V**, **Corban J** (2017) Topical medical cannabis: a new treatment for wound pain—three cases of pyoderma gangenosum. *J Pain Symptom Manage*, **54**(5), 732–6.
37. **Kintzel P**, **Knol J**, **Roe G** (2018) Intravenous lidocaine administration as twice daily bolus and continuous infusion for intractable cancer pain and wound care pain. *J Palliat Med*, **20**(20), 1–5.
38. **Page N**, **Nirabhawane V** (2018) Intranasal ketamine for the management of incidental pain during wound dressing in cancer patients: a pilot study. *Indian J Palliat Care*, **24**(1), 58–60.
39. **Riot S**, **de Bonnecaze G**, **Garrido I**, **Ferron G**, **Grolleau J-L**, **Chaput B** (2015) Is the use of negative pressure wound therapy for a malignant wound legitimate in a palliative context? The concept of NPWT *ad vitam*: a case series. *Palliat Med*, **29**(5), 470–3.
40. **Naylor W** (2002) Malignant wounds: aetiology and principles of management. *Nurs Stand*, **16**(52), 45–53.
41. **da Costa Santos CM**, **deMattos Pimenta CA**, **Nobre MRC** (2010) A systematic review of topical treatments to control the odor of malignant fungating wounds. *J Pain Symp Manage*, **39**(6), 1065–76.
42. **George R**, **Prasoona T**, **Kandasamy R** *et al.* (2017) Improving malodour management in advanced cancer: a 10-year retrospective study of topical, oral and maintenance metronidazole. *BMJ Support Palliate Care*, **7**(3), 286–91.
43. **Ker K**, **Beecher D**, **Roberts I** (2013) Topical application of tranexamic acid for the reduction of bleeding. *Cochrane Database Syst Rev*, **7**, CD010562.
44. **Reingold IM** (1966) Cutaneous metastases from internal carcinoma. *Cancer*, **19**, 162–8.
45. **Lookingbill DP**, **Spangler N**, **Helm KF** (1993) Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. *J Am Acad Dermatol*, **29**(1), 228–36.

Chapter 16

Urological symptoms and complications in palliative care

José Pereira

Attitude

To enable each learner to:

- Demonstrate person-centred, individualized care for patients with urinary symptoms and complications related to advanced disease.
- Recognize the significant distress that urinary symptoms may cause patients with palliative care needs, across the illness trajectory from diagnoses to end-of-life phase.

Skills

To enable each learner to:

- Manage complications such as haematuria, lower and upper urinary tract (UUT) obstructions, and long-term bladder catheterization.
- Identify patients who could benefit from more invasive interventions to control symptoms and improve quality of life.
- Ensure timely referral to specialized services such as urological and interventional radiology for patients with complex needs.

Knowledge

To enable each learner to:

- Describe some common urinary-related symptoms and complications experienced by patients with advanced disease and their impact on the quality of life.
- Describe treatment options to manage haematuria, urethral and ureteric obstruction, and entero- and vagino-vesico fistulae.
- Describe first- and second-line treatment options to manage bladder-related pain and spasms, including strangury and tenesmus, as well as urgency.

Introduction

Genitourinary symptoms are relatively common in patients with progressive, advanced diseases. This chapter focuses on the more frequent or challenging urological symptoms associated with cancer. Urinary tract infections (UTIs) are outside the scope of this chapter.[1]

Individualized approaches are recommended in managing urological symptoms, taking into consideration the personal circumstances of the individual patient in order to avoid burdensome

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treatment or missed opportunities to palliate. If life expectancy is uncertain, but guarded, a therapeutic trial may be considered, with both patient and family agreeing that treatment will be stopped if there is no improvement in symptoms.

Case 16.1

J.C. is a 68-year-old male with Stage IVB transitional cell (urothelial) carcinoma of the bladder, with pelvic and abdominal lymphadenopathy, invasion of the pelvic wall, and metastatic nodules in the lungs (T4, N3, M1). Two years previously, at diagnosis, he was treated for Stage II cancer with a partial cystectomy, preceded by neo-adjuvant chemotherapy with cisplatin, methotrexate, and doxorubicin. The chemotherapy resulted in significant adverse effects. When his cancer recurred a few months ago, he was treated with pembrolizumab immunotherapy. The cancer has progressed despite this treatment. He is on controlled-release oral morphine at 90 mg orally twice a day for pelvic pain. Until a few days ago, he seldom required breakthrough short-acting morphine, prescribed at 20 mg q1h PRN, but is now taking 4–5 doses a day.

He has haematuria and increasing pelvic pain. The haematuria started a few days ago as frank blood in the urine with clot streaks. He is distressed. He rates his pelvic pain on a numerical assessment scale as 6/10, on average. His Palliative Performance Scale v2 (PPSv2) is 60%; he is ambulant but has given up his work because of increasing fatigue. Despite good appetite and food intake, he has lost 3 kg over 2 months.

Question 1. What is the most likely cause of haematuria in patients with advanced cancer?

In new-onset haematuria, it is important to first determine whether the bleeding is from the upper or lower urinary tract. Primary or metastatic malignancies of the kidneys and ureters, such as renal cell or urothelial carcinomas, are more common causes of bleeding from the UUT. In rare cases, bleeding may originate from renovascular, pyelovascular, and ureterovascular fistulae. These fistulae are often iatrogenic or from procedures such as percutaneous nephrolithotomy or nephrostomy tubes, prolonged ureteral or vascular stenting, or previous radiation treatment. Lower urinary tract sources of bleeding include prostate, urothelial, and non-urothelial bladder cancers, invasion of the bladder by gynaecological or colorectal malignancies, haemorrhagic cystitis secondary to radiation, chemotherapy (especially ifosfamide and cyclophosphamide), or urethral trauma following bladder catheterization or cystoscopy. Nephrolithiasis and UTIs are other causes.

Frailty, poor wound healing, bleeding diatheses caused by nutritional deficiencies, anticoagulant medications, and medications such as non-steroidal anti-inflammatories also increase the risk of bleeding in patients with advanced disease.

For J.C., the most likely cause of his haematuria is progression of the bladder cancer, but this needs to be confirmed and contributory factors identified.

Question 2. What is the impact of haematuria in patients with advanced disease?

Haematuria is distressing for patients with advanced disease and their families. As little as 1 ml of blood can produce a visible colour change in 1 litre of urine.[2] The redness does not necessarily correlate with the total amount of blood loss but does indicate the bleeding rate. At end of life, gross haematuria can be particularly challenging as treatment options are sometimes more

limited. The burden of invasive treatments may outweigh the potential benefits at this phase, and relief of accompanying symptom burden becomes paramount.[3]

Depending on the aetiology, location, severity, and duration, haematuria may be accompanied by pain and other symptoms and complications such as clots, infection, strangury, or anaemia. Anaemia could, in turn, exacerbate asthenia or dyspnoea and may, in select cases, require periodic blood transfusions. If severe or untreated, clot retention could lead to secondary obstructive uropathy. Severe bleeding can be life-threatening if control is unsuccessful or not possible. In the context of advanced disease with limited life expectancy, a patient's goals of care may make comfort without invasive work-up or treatment more appropriate.

Question 3. How will you assess J.C. at this time?

A detailed history and focused physical examination are needed to help establish bleeding severity and origin. Recurrent chronic bleeding may point towards a predisposing condition or process with a slow evolution, while new bleeding may herald disease progression or new complications. Bleeding mainly at the start of urination may indicate a ureteral source, while haematuria only at the end of voiding in males may suggest a prostatic origin. Bleeding throughout could originate in the bladder or UUT. The extent and severity of bleeding needs to be assessed, as this has important therapeutic implications. The presence of blood clots also increases the risk of urinary obstruction, which could lead to obstructive uropathy.

A review of systems, medications, and concurrent medical problems is essential. Medications such as non-steroidal anti-inflammatories and anticoagulants could contribute to haematuria. Other underlying factors, such as thrombocytopenia from extensive bone metastases and bone marrow infiltration, complications of anticoagulant treatment, or inherited or acquired bleeding diathesis such as von Willebrand's disease, could exacerbate the situation.

A simple bedside dipstick heme test may help confirm the presence of blood.[2] Dark urine may result from conditions such as bilirubinaemia, beet ingestion, and medications such as flutamide, metronidazole, and vitamin B complex, which would be accompanied by a negative heme test. The presence of frank blood, as in the case of J.C., makes a urine dipstick test redundant. A urine culture should be considered when haematuria is accompanied by symptoms of infection.

Although J.C. has advanced disease, his life expectancy may still be in the order of months if bleeding can be controlled. A more extensive work-up may be warranted and could include cystoscopy and ureteroscopy. Computed tomography (CT) urography will image the UUT and requires the injection of intravenous (IV) contrast material. Magnetic resonance (MR) urography, when available, has better resolution than CT urography and can, in some cases, be done without IV contrast, making it more suitable for patients with renal impairment.[4] Urography with CT or MR is replacing conventional X-ray urography (IV pyelogram). It also allows for better visualization of other structures. Retrograde pyelography, where a radiocontrast agent is injected via ureteroscopy into the ureter to visualize the ureter and kidney with fluoroscopy or radiography, may be used when CT urography is contraindicated or inconclusive. However, there are few evidence-based guidelines to help select between these modalities.[3]

Case 16.1 (continued)

J.C. shows no symptoms or signs of urinary obstruction or infection. He does not have life-threatening bleeding that would necessitate haemodynamic stabilization and transfusion. In discussion, J.C. enquires about the extent of the disease, prognosis, possible causes for haematuria, potential benefits and burden of work-up and treatment options, and ultimately his goals of care. He recognizes there are no further treatments to control his cancer. He confirms a Do-Not-Resuscitate (DNR) code status. He is open to undergoing

further tests and treatments to control the bleeding. You increase his morphine dose to manage his pain, exclude a coagulopathy problem with blood work, and refer him to his urologist. A cystoscopy is undertaken, which shows an exposed vessel in an ulcerating bladder mass as the source of bleeding. Urology decides a CT urogram and other investigations are not needed at this time.

Question 4. How might J.C.'s haematuria be managed?

Cystoscopy allows for endoscopic fulguration or cauterization. In some cases, cystoscopy is not possible or not available, or is declined. In other cases, bleeding may continue despite endoscopic fulguration. If haematuria is not immediately life-threatening, radiation may be useful.[5,6] Simultaneous significant reductions in pain were also reported in radiation treatment studies.[5,6]

If the aforementioned modalities are unsuccessful and bleeding is severe, transarterial embolization (TAE) with interventional radiology can be considered. In life-threatening situations, where the goals are life prolongation, other options include surgical ligation of the hypogastric arteries and palliative cystectomy with urinary diversion via an ileal conduit.[5] Urinary diversion through cutaneous nephrostomies or ureterostomies, without palliative cystectomy, can be considered in refractory cases where gross haematuria is causing bladder tamponade, severe pain, or obstructive uropathy. This may further reduce bleeding by preventing the thrombolytic enzyme urokinase (found in urine) from coming into contact with the bladder mucosa.[6] If the source of bleeding is renal, endoscopic or endovascular interventions would also be appropriate in select cases, with palliative nephrectomy or nephroterectomy as last-resort options in patients with good functional status.

Case 16.1 (continued)

The urologist proceeds to cauterize the vessel with diathermy. This immediately stops the bleeding and J.C. is discharged home. He does well for several weeks. One month later, mild haematuria and pain recur. He receives palliative radiotherapy, which stops the bleeding and reduces the pain.

Over the following 2 months, his functional status gradually declines. He experiences gross haematuria with blood clots, accompanied by increasing suprapubic pain and difficulty urinating. The physician doing the home visit uses portable point-of-care ultrasound (POCUS) to confirm urinary retention, likely from blood clots. The home care team reviews his goals of care and a decision is made to insert a Foley urinary catheter, which immediately relieves his pain. He agrees to be transferred to the local inpatient palliative care unit, with the hope of returning home once the haematuria is controlled. He appears uncomfortable, severely cachectic, and pale and has a palpable mass in the suprapubic area. He is bedridden, with a PPS score of 30%.

Question 5. How should J.C. be managed at this time?

Given the overall functional status and his goals of care, bladder irrigation to evacuate the clots, by way of hand or manual irrigation, intermittent manual irrigation, or continuous bladder irrigation (CBI), would be an appropriate and practical option.[6] A repeat cystoscopy could be considered to identify the bleeding source, evacuate clots, and fulgarize the bleeding source with electrocautery or laser coagulation. J.C. elects to proceed with a saline washout, followed by CBI. Bladder irrigation does not per se cause haemostasis; its main role is to prevent clot retention.

Bladder irrigation can be uncomfortable, primarily from bladder detrusor muscle spasm, and adjustments to analgesic regimens may be needed. If an indwelling catheter is required for

longer-term irrigation but causes significant discomfort, a trial of belladonna and opium suppositories rectally three to four times a day is suggested.[6] Oxybutynin is another option.

Case 16.1 (continued)

J.C.'s haematuria resolves 3 days later, and after a successful trial of spontaneous voiding, he is discharged home.

Question 6. What would one do if bladder irrigation was unsuccessful in controlling bleeding?

For persistent bladder bleeding, whether from malignancy, radiation, or chemotherapy-related cystitis, several adjunct therapies can be considered and added to the CBI irrigant.[7] Epsilon aminocaproic acid is used first line, with reported success rates of up to 90%, and second-line agents include alum 1–2%, formalin, and 1% silver nitrate.[7,8]

For J.C., more invasive options were ruled out, based on goals of care. Options such as transurethral coagulation, external beam radiation, TAE, or hypogastric artery ligation could be considered in select cases.[8]

Question 7. What if the haematuria were from causes other than a bladder tumour or from other sources?

Additional therapies may be considered in select cases for haematuria from other sources. For haematuria of prostatic origin, inflating the balloon of a Foley catheter after bladder insertion and applying gentle traction can achieve tamponade. Medical management with finasteride, a 5-alpha reductase inhibitor, or androgen deprivation are long-term options. With haematuria from haemorrhagic cystitis, intravesically infused hyperbaric oxygen constitutes a third-line option but requires multiple treatments and is not readily available.

For upper genitourinary tract haematuria, modalities such as external beam radiotherapy, systemic treatment with aminocaproic acid, endoscopic surgery (resection or coagulation), arteriography with embolization, or surgical ligation of major vessels are options, depending on the nature of the bleeding and the patient's goals of care and life expectancy.

Question 8. How would you manage strangury and/or tenesmus if J.C. was experiencing these?

Strangury is slow, painful urination that usually occurs as a result of spasms of the bladder or the urethra. Tenesmus, on the other hand, is a constant sensation of fullness or incomplete relief during urination or defecation and is often accompanied by pain and/or strangury.[9]

Strangury often presents alongside symptoms such as dysuria, frequency, and urgency, and hence can be mistaken for a UTI. The differential diagnosis for strangury in palliative care includes UTI, bladder or prostate cancers or tumours, gynaecological or rectal cancers invading the bladder, bladder inflammation or cystitis, blood clots in the bladder, radiation fibrosis, urethral stricture, urinary retention, and urinary calculus. Overinflation of a Foley catheter or excess balloon size are often overlooked as possible causes. Investigations to identify the cause of new-onset strangury may include laboratory work-up with urinalysis or urine cytology, bladder scan, imaging such as ultrasound of the urinary tract, or more invasive procedures such as cystoscopy.

The initial step in management is to identify any reversible or treatable cause. If this is not possible or insufficient, symptomatic management is indicated.[9] The mainstay of treatment is non-opioid and opioid treatments, depending on pain severity. Control of bladder spasms can be attempted with opium and belladonna suppositories, anticholinergic agents, and smooth muscle relaxants such as tolterodine and oxybutynin, or corticosteroids. With severe strangury, insertion of an indwelling urinary catheter can bring relief for some, but aggravation for others.

The differential diagnosis of urinary tenesmus is similar to that for strangury. Definitive treatment is managing the underlying malignancy with chemotherapy or radiation therapy, when possible. If not feasible, then the goal is to control the symptom. Tenesmus can be distressing and cause considerable anxiety. Anxiety, in turn, can exacerbate tenesmus. Symptomatic treatment can be challenging. While opioids, anticholinergic drugs, calcium channel blockers, phenothiazines such as chlorpromazine, and benzodiazepines have been used, with mixed results, to manage defecation-related tenesmus, these results do not necessarily transfer to urinary tenesmus. Intractable tenesmus, especially if accompanied by severe pain, may require anaesthetic procedures such as bilateral lumbar sympathetic, superior hypogastric, or intraspinal blocks.[6,9]

Case 16.2

L.P. is a 48-year-old woman with Stage IV primary cervical squamous carcinoma. A few years previously, at diagnosis, she had Stage III cervical cancer and was treated with radiation therapy [intracavitary radiation therapy and external beam radiation therapy (EBRT)] and concomitant chemotherapy with cisplatin/fluorouracil (5FU). Unfortunately, the cancer progressed despite treatment. Staging examinations confirmed extension of the cancer into the pelvic wall and pelvic organs, including the bladder and rectum, with extensive pelvic and para-aortic lymphadenopathy. She was offered palliative chemotherapy with cisplatin and paclitaxel but did not tolerate these, and treatment was stopped. She presents now with increasing suprapubic pain (which she rates at 7/10, on average), vaginal leakage of urine, and vaginal malodour. She is on controlled-release hydromorphone 9 mg orally twice a day and, over the past week, using 3–5 PRN breakthrough doses per day of short-acting hydromorphone 1 mg orally.

Question 9. What is the most likely cause of L.P.'s symptoms?

L.P. most likely has a vesicovaginal fistula (VVF). Patients with advanced cancer, particularly gynaecological, urogenital, and colorectal cancers, are at increased risk of developing VVF and vesicoenteric fistulae (VEF). A number of factors contribute to this, including local invasion of the tumour, prior pelvic surgery, prior brachytherapy or EBRT, infection, poor nutrition, and compromised wound-healing ability.[10] In rarer cases, fistulae may be caused by underlying inflammatory conditions such as severe diverticulitis and Crohn's disease.

Fistulae involving the urinary tract, such as VVFs, give rise to a number of symptoms. In addition to suprapubic pain, dysuria, vaginal leakage, and malodorous urine with which L.P. presented, they can produce pneumaturia, pelvic and skin infections, chronic UTIs, perineal rash, and skin breakdown. VEFs are rarer and, in addition to pain, frequency, and chronic UTIs, can present with faecaluria, diarrhoea, and tenesmus.[10]

Fistula formation is precipitated by EBRT or brachytherapy for intestinal, gynaecological, or urological malignancies. The fistulae may develop many months and even years after the treatment. L.P.'s fistula is most likely due to direct tumour invasion.

Question 10. How would you assess L.P. at this time?

More information is needed to elucidate the characteristics and evolution of the pain. This includes onset, course, accompanying bleeding or infections, and other concurrent symptoms. The presence of other fistulae needs to be explored. Enterovesical fistulae often include a combination of suprapubic pain, frequency, dysuria, and tenesmus—referred to as Gouverneur syndrome.

Evaluation of L.P.'s mood and psychosocial status is essential. Complications caused by fistulae, such as pain, recurrent infections, incontinence, stranguria, faecaluria, and malodour, can have a devastating impact on quality of life. Regular self-catheterization or urinary diversion procedures such as cystostomies and nephrostomies add to patients' sense of burden and reduced self-esteem.

A physical examination should include overall level of comfort, functional and nutritional status, signs of anaemia or infection, and an examination of the abdomen and perineum. A pelvic examination should only be conducted if it will not cause additional pain or discomfort and is expected to shed useful information and inform the treatment planning. Sometimes, imaging such as CT scanning can provide more useful information in these situations than a pelvic examination.

Case 16.2 (continued)

History reveals that the vaginal leaking started about a week after the pelvic pain intensified. Her urine is darker and, on occasion, blood-streaked. She has reduced appetite and increasing weight loss. Her quality of life is significantly compromised, and she is feeling very depressed. She avoids social contact and hardly leaves home. Physical examination reveals early signs of cachexia and a malodorous discharge from her vagina, with perineal excoriation. Labs reveal a UTI with haematuria, anaemia (haemoglobin 9.0 g/dl), mild leucocytosis (white blood cell count 13.0 x 10^9/l), and mild renal impairment [creatinine clearance (CCr) 130 ml/min, blood urea nitrogen (BUN) 9 mmol/l]. Albumin is reduced (28 g/l). Her PPS is 60%. A decision is made to omit pelvic gynaecological examination but to proceed with further investigations.

Question 11. What investigations should be considered at this time?

If diagnostic tests are deemed appropriate, a urinalysis in the context of a VVF commonly reveals debris, haematuria, and UTI. If a UTI is present, culture for sensitivity testing may be required but may identify mixed flora or *Escherichia coli*. Recurrent UTIs are common with VEF and VVF. A full blood count, creatinine and estimated CCr, BUN, and electrolytes provide important baseline and treatment planning information.

Imaging can be useful for assessment and treatment planning. Which modality and technique to select depends largely on history and physical examination; a combination of techniques is sometimes required.[11] MR imaging is useful both for disease staging and for detection of complications such as fistula formation. If an enteric fistula is suspected, CT scanning can be augmented with contrast material administered rectally. A CT urogram can be considered if a vesicoureteral or ureteroenteric fistula is suspected. Endoscopy with cystoscopy and colonoscopy may also be confirmatory in select cases.

Case 16.2 (continued)

L.P. decides to proceed with a CT cystogram. The test is scheduled in 3 days' time. In the meantime, she is experiencing significant pain.

Question 12. How would you manage L.P.'s pain at this time?

It would be reasonable to manage L.P.'s pain empirically, while awaiting imaging. Based on the information at hand, the pain is most likely associated with disease progression, including the development of a VVF and a UTI. Opioids are increased (see pain management in Chapter 2) and she is treated with an oral broad-spectrum antibiotic for her UTI.

Case 16.2 (continued)

A CT cystogram confirms a moderate-sized VVF, significant tumour enlargement with further encroachment into the superior bladder, and significant peri-tumoral oedema. The right ureter and right kidney show early signs of hydroureter and hydronephrosis. You disclose these findings to L.P., provide supportive counselling, and engage in goals of care discussions.

Question 13. What would be the key considerations in L.P.'s management at this time?

A key consideration in management is determining whether a VVF is simple or complex. Simple VVFs usually have a diameter of less than 0.5 cm, are single, and occur in non-irradiated tissue. Complex VVFs are larger, may include multiple tracts, and occur in previously irradiated tissue.[12]

L.P.'s fistula is complex and formal surgical fistula repair, while an option in select cases, is not feasible in this case. Surgical or spontaneous closure would be unlikely. Palliative goals would include symptom management and containment of complications like leakage and skin damage. Prolonged antibacterial therapy for symptom relief can be considered in some patients who experience chronic UTIs from fistulae.

Diversion of urine using a Foley or suprapubic urinary catheter may help palliate. In advanced cases, where a urinary catheter is not possible, bilateral nephrostomy tubes may be considered, but some patients may find this burdensome. Surgical diversion with an ileal conduit or formal fistula repair could be appropriate in select patients whose disease is more confined and functional status is less compromised. In the case of VEFs, a diverting colostomy or rectal stent may be considered in severe cases.

Evolving renal impairment and hydronephrosis from ureteric obstruction may also need attention. Conservative management by monitoring renal function and trialling a course of dexamethasone to reduce peri-tumoral oedema or debulking surgery or ureteric stents may be considered.

Case 16.2 (continued)

After discussing the options, L.P. chooses Foley catheter insertion and dexamethasone 4 mg po once a day for 2 weeks, followed by gradual tapering, in hopes of reducing compression of the ureter and improving pain control. Six weeks later, L.P. presents with increasing nausea. Blood tests reveal worsening renal function. Ultrasound reveals worsening right hydroureter and hydronephrosis, with loss of kidney parenchyma, and new left hydroureter.

Question 14. What are the common causes of upper urinary tract obstruction in the palliative care context?

In this context, UUT obstruction is most commonly caused by intraluminal masses or, as in the case of L.P., compression or invasion by gynaecological, colorectal, retroperitoneal, or other cancers or metastasis.[8] Prior radiation to the region may also cause fibrosis or strictures of the ureters. Benign causes, such as calculi and retroperitoneal fibrosis, are less common. Classifying causes into intraluminal versus extra-luminal can be useful. Intraluminal sources of blockage include urinary tract cancer such as transitional cell carcinoma, strictures, or stones, while extra-luminal are usually cancers compressing the ureters or bladder.

Question 15. How is UUT obstruction assessed and managed in the palliative care setting?

The extent to which one works up an obstruction depends on the overall context and goals. If investigations are deemed appropriate and ureteral obstruction is suspected, preliminary studies could include urinalysis, renal ultrasound, and renal function labs.[8] Additional imaging with CT urogram may be required, especially if the source of obstruction is unknown and more invasive procedures would be appropriate.

The two main invasive options for tumour or radiation therapy-related causes are endoscopically placed ureteric stents or percutaneous nephrostomy tubes. Ureteric stent placement usually requires general anaesthesia, while percutaneous nephrostomy placement can be done by interventional radiology with general anaesthesia or conscious sedation. Placement risks include bleeding and vascular injury (especially in patients with coagulopathy problems or on anticoagulation treatments), infection, and discomfort. Ureteral stents may cause colicky pain, frequency, and dysuria. With nephrostomy tubes, some patients may find managing the bags and the social stigma associated with external bag drainage too burdensome. Bilateral nephrostomy tubes can be uncomfortable for some patients.

Ureteral stents are associated with higher failure rates in the setting of malignant compression,[13] but metallic stents may have fewer failure rates. If ureteral stents fail, percutaneous nephrostomy placement can be considered. Evidence is inconclusive as to which procedure is superior or should be performed first. Considerable variation in terms of quality of life and survival benefits have been reported for both.[6,14,15,16] Nephrostomy tubes and ureteric stents usually require exchange every 3 months. Blockage by calcifications and encrustation may require replacement sooner.

Question 16. How would you manage ureteral obstruction and early obstructive uropathy for L.P. at this time?

In L.P.'s case, the source of the obstruction is known and a decision is made to forgo further imaging and insert a ureteric stent on the right side. This resolves the nausea and her renal function improves significantly.

Case 16.2 (continued)

L.P. does relatively well for 4 months with few urinary symptoms, but her overall functional status continues to decline as a result of disease progression. She becomes bedridden and cachectic, with a PPS of 20%. She is being cared for at home and her wish is to stay home. She develops severe nausea and starts vomiting. Blood work done via a mobile laboratory shows severe renal impairment.

Question 16. What is happening, and how would you manage L.P. at this time?

While there may be several possible causes for her nausea, blockage of the ureteric stent should be considered. This could be confirmed with POCUS in the home, if available. If her functional status were better and her goals of care different, consideration could be given to proceeding with bilateral nephrostomy placement. L.P. decides to not proceed with any further investigations or urological interventions and chooses to focus on controlling her nausea and symptoms and to be cared for at home until her death (see Chapter 19 on the last hours and days).

Case 16.3

O.F. is a 62-year-old man diagnosed 3 years previously with Stage IIIB prostate adenocarcinoma, with extraprostatic extension but no involved lymph nodes or metastases. He originally underwent EBRT and hormonal treatment with leuprolide, a luteinizing hormone-releasing hormone (LH-RH) agonist. Unfortunately, 5 months ago, he was found to have Stage IVB disease recurrence (pelvic and bone metastases). He was started on palliative chemotherapy with docetaxel. There is evidence of further disease progression despite the treatment. He received palliative radiotherapy to a metastatic lumbar lesion and is on morphine. He now presents with suprapubic discomfort, frequency, urge incontinence, and urgency. His PPS is 70%.

Question 17. What may be causing urinary incontinence?

Urinary incontinence (UI), involuntary leakage of urine, is a relatively common complication in the palliative care context.[17] There are several causes for urge UI, including overactivity of the bladder detrusor muscle from UTI, intrinsic or extrinsic tumours, radiation cystitis and urethritis, medications such as diuretics, sacral nerve lesions, and metabolic causes such as hypercalcaemia, uraemia, and diabetes mellitus. Stress UI, where leakage occurs on effort, sneezing, or coughing, may be caused by sphincter damage after radical prostatectomy. Some patients experience both urge and stress UI (mixed UI). Overflow incontinence, when urine leaks because of larger-than-normal bladder capacity or filling, may be caused by bladder outlet obstruction such as in benign or malignant prostate enlargement. Patients present often with nocturnal enuresis at first.[17] Continuous or total incontinence, which presents as continuous involuntary loss of urine, is most commonly seen with direct tumour invasion of the urethra or bladder and fistulae. Stool impaction may cause UI.

In the case of O.F., the UI is most probably being caused by the prostate cancer irritating the bladder or obstructing the bladder outlet, or a combination of both. A UTI needs to be ruled out and further investigations are needed to better understand the problem and direct treatment.

Question 18. How will you assess these symptoms further at this time?

History should rule out constipation or faecal impaction, which are relatively common causes of urinary retention in this patient population. On physical examination, bladder outlet obstruction can manifest as suprapubic tenderness and fullness. Examination should include a rectal and vaginal examination (women) and a neurological examination of sacral sensation and anal reflexes. Stress testing by coughing or the Valsalva manoeuvre with a full bladder can help identify stress UI. Baseline investigations could include some basic blood work (creatinine, BUN) and urinalysis

with or without culture. The post-void residual volume could be assessed using in-and-out catheterization or bladder ultrasound scan. A post-void residual volume greater than 100 ml suggests bladder outlet obstruction. This initial assessment will inform further investigations and needs to be individualized. Renal ultrasound may show hydroureters and/or hydronephrosis; CT or MRI can help to determine progression of disease, while cystoscopy can be useful in diagnosing a bladder tumour or prostatic cancer invasion.

O.F.'s rectal examination reveals an enlarged, hard prostate and a suprapubic mass. The bladder scan reveals a full bladder and a residual volume of 200 ml post-voiding. A decision is made to proceed with CT imaging, which confirms bladder outlet obstruction caused by a large prostate tumour and disease extension into the pelvis. There is no hydroureter or hydronephrosis.

Question 19. How will you manage O.F.'s urinary outlet obstruction at this time?

Management of bladder outlet obstruction ranges from open surgery and endoscopic interventions to urethral or suprapubic catheterization and medications. Selection is based on the cause of the obstruction and the patient's prognostic time course, overall functional status, and wishes. For benign prostatic enlargement/hypertrophy (BPH), pharmacological management with an alpha-antagonist (α1-adrenoreceptor antagonist) such as tamsulosin (400 mg po daily) or alfuzosin (2.5–10 mg po daily), or a 5α-reductase inhibitor (finasteride 5 mg po daily), is reasonable; 5α-reductase inhibitors have an onset of action of up to 3 months. They are therefore less useful in patients with limited life expectancy and are not effective in improving obstruction from prostate cancer.

Transurethral prostate resection (TURP) or incision could be considered for benign or malignancy-related obstruction if pharmacological approaches fail or are suboptimal. Limited TURPs can be palliative interventions in patients with advanced prostate cancer to reduce post-TURP incontinence risk. There is a risk of non-healing, particularly with previous radiotherapy (external beam or brachytherapy).

For urethral strictures, which are not uncommon post-prostate resection and radiation therapy, urethral dilation, direct vision internal urethrotomy (DVIU), or catheterization with an indwelling catheter or suprapubic catheter can be considered. Urethral stents appear to have a limited role. Primary urethra reconstruction surgery is usually not an option.

Palliative surgery may be considered for select patients with large pelvic tumours related to colorectal, gynaecological, and sarcoma cancers that cause severe urinary symptoms as a result of compressing or invading the bladder. Urinary diversion using an ileal conduit, with or without more extensive surgery such as cystectomy, can be considered in select patients.

Question 20. How would you have managed O.F. if he had presented in severe distress with acute outlet obstruction?

Urgent catheterization would be required. An indwelling Foley or Coudé tip urethral catheter or a suprapubic catheter could be used. Electrolytes and urinary output should be monitored closely post-catheterization because of the risk of post-obstructive diureses (urinary output of greater than 200 ml/hour). Following resolution of the acute episode, more definitive treatment of the underlying problem would be required. If ongoing catheterization is required, consideration should be given to switching from an indwelling catheter to clean intermittent catheterization (CIC), if the patient is able.

Question 21. How would you manage detrusor overactivity, urge urinary incontinence, and stress urinary incontinence in the palliative care setting that is not related to malignancy?

Basic lifestyle and toileting changes for detrusor overactivity and UI include adjusting the timing or amount of fluid intake, scheduled toileting, providing a bedside commode, or pads and special undergarments. Anticholinergic medications such as oxybutynin (2.5–5 mg twice to three times a day), oxybutynin slow-release (5–30 mg po once a day), tolterodine (2 mg po twice a day), or tolterodine slow-release (2–4 mg once a day) can be considered. These M1 and M3 muscarinic receptor antagonists and direct muscle relaxants are generally effective but can be associated with the usual side-effects of antimuscarinic drugs. Side-effects may be reduced with the controlled-release formulations. Indwelling urethral catheters should be avoided for urge UI and detrusor overactivity as they exacerbate the problem. Duloxetine (20–40 mg po daily) can also be considered. Palliative catheterization may provide some relief in refractory cases.

Question 22. How would you manage long-term catheterization in the palliative care setting?

Long-term urinary catheterization is a relatively common intervention in the palliative care setting, especially in patients with advanced disease. Catheterization should be used judiciously and only when necessary, rather than as a convenience for care providers. Indwelling catheters cause recurrent UTIs, urethritis, and bladder irritation. The risk for a catheter-related infection increases 10% for every day of catheterization versus 3% for CIC.[8] Suprapubic catheters may provide a reasonable alternative to urethral catheters in some cases.

Asymptomatic bacteriuria associated with long-term indwelling catheters is common and does not require routine urine culturing or treatment. Antibiotic treatment is reserved for symptomatic catheter-associated infections, plus at least 10^5 colony-forming units with one or two predominant organisms. Prophylactic long-term antibiotic therapy may be considered in cases of recurrent symptomatic infections. Catheters should be changed every 3 to 4 weeks, using sterile techniques. Silicone catheters, or silicone-coated latex catheters, are preferred over latex rubber catheters, as they are associated with less catheter encrustation. Silver alloy-coated catheters do not reduce the risk of UTIs or encrustation over the long term.

Conclusion

Urological symptoms can have a devastating impact on quality of life for patients receiving palliative care. Overall, clinical care should be individualized in patients with advanced disease. Many factors should be considered when establishing the extent to which one investigates and treats symptoms. A number of management options are available.

References

1. **Pereira J**, **Watanabe S**, **Wolch G** (1998) Retrospective review of the frequency of infections and patterns of antibiotic utilization on a palliative care unit. *J Pain Symptom Manage*, **16**(6), 374–81.
2. **Gadler T**, **Keedy M**, **Rivas N** (2010) A case of hematuria. *Adv Emerg Nurs J*, **32**(1), 30–41.
3. **Groninger H**, **Phillips JM** (2012) Gross hematuria: assessment and management at the end of life. *J Hosp Palliat Nurs*, **14**(3), 184–8. doi:10.1097/NJH.0b013e31824fc169

4. **O'Connor O**, **McLaughlin P**, **Maher MM** (2010) MR urography. *Am J Roentgenology*, **195**(3), W201.
5. **Delgal A**, **Cercueil JP**, **Koutladi N** *et al.* (2010) Outcome of transcatheter arterial embolization for bladder and prostate hemorrhage. *J Urol*, **183**, 1947–53.
6. **Tsushima T**, **Miura T**, **Hachiya T** *et al.* (2019) Treatment recommendations for urological symptoms in cancer patients: clinical guidelines from the Japanese Society for Palliative Medicine. *J Palliat Med*, **22**(1), 54–61.
7. **Abt D**, **Bywater M**, **Engeler DS**, **Schmid HP** (2013) Therapeutic options for intractable hematuria in advanced bladder cancer. *Int J Urol*, **20**(7), 651.
8. **Lee OT**, **Wu JN**, **Meyers FJ**, **Evans CP** (2015) Genitourinary aspects of palliative care. In: Cherny NI, Fallon MT, Kaasa S, Portenoy RK, Currow DC (eds.) *The Oxford Textbook of Palliative Medicine*, 5th edn, pp. 441–6. Oxford University Press, Oxford.
9. **Ang SK.** Tenesmus, strangury and malodor. In: Walsh TD, Caraceni A, Fainsinger R, *et al.* (eds.) *Palliative Medicine*, 1st edn, pp. 946–50. Elsevier Publishers, New York, NY.
10. **Golabek T**, **Szymanska A**, **Szopinski T** *et al.* (2013) Enterovesical fistulae: aetiology, imaging and management. *Gastroenterol Res Pract*. doi: 10.1155/2013/617967
11. **Narayanan P**, **Nobbenhuis M**, **Reynolds KM** *et al.* (2009) Fistulas in malignant gynecologic disease: etiology, imaging, and management. *Radiographics*, **29**(4), 1073–83. https://doi.org/10.1148/rg.294085223
12. **Angioli R**, **Penalver M**, **Muzii L** *et al.* (2003) Guidelines of how to manage vesicovaginal fistula. *Crit Rev Oncol Hematol*, **48**, 295–304.
13. **Kamiyama Y**, **Matsuura S**, **Kato M** *et al.* (2011) Stent failure in the management of malignant extrinsic ureteral obstruction: risk factors. *Int J Urology*, **18**(5), 379–82.
14. **Dienstmann R**, **da Silva Pinto C**, **Pereira MT** (2008) Palliative percutaneous nephrostomy in recurrent cervical cancer: a retrospective analysis of 50 consecutive cases. *J Pain Symptom Manage*, **36**, 185–90.
15. **Kanou T**, **Fujiyama C**, **Nishimura K** *et al.* (2007) Management of extrinsic malignant ureteral obstruction with urinary diversion. *Int J Urology*, **14**, 689–92.
16. **Emmert C**, **Raßler J**, **Köhler U** (1997) Survival and quality of life after percutaneous nephrostomy for malignant ureteric obstruction in patients with terminal cervical cancer. *Arch Gynecol Obstet*, **259**(3), 147–51.
17. **Giri SK**, **Flood HD** (2008) Incontinence: urine and stool. In: Walsh TD, Caraceni A, Fainsinger R *et al.* (eds.) *Palliative Medicine*, 1st edn, pp. 898–905. Elsevier Publishers, New York, NY.

Chapter 17

Mouth care

Samir Azzaria, Marie-Andrée Fournier, and Mélanie Simard

Attitude

To enable each learner to:

- Consider the importance of prevention and early recognition of oral problems in patients living with cancer.
- Realize the importance of an interprofessional approach to mouth care, involving healthcare professionals, patients, and caregivers.
- Plan strategies to enhance oral health in palliative care patients.

Skills

To enable each learner to:

- Diagnose and treat common oral pathologies.
- Assist in the education of patients and caregivers about oral care.

Knowledge

To enable each learner to:

- Recommend measures for maintaining good oral hygiene.
- Cite and describe the multiple oral problems that can affect patients with advanced illness.
- Propose appropriate treatment plans.

Case 17.1

D.L., a 60-year-old man, has just received a diagnosis of laryngeal squamous cell carcinoma for which concomitant chemoradiation is indicated. He will receive cisplatin 100 mg/m^2 on days 1, 22, and 43 of his radiation treatments. His current medications include oral hydromorphone 1 mg every hour, as needed, for throat pain. He has no allergies.

Question 1. How common and important are oral problems in patients with palliative care needs?

Oral health is an indicator of the general condition of a patient, especially at the end of life.[1] Experienced caregivers can detect specific oral conditions through scent and sight. Most

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patients will experience at one point or another dry mouth, pain, dysphagia, taste disturbance, or infection.[2] The primary illness and the medical history, as well as the treatment, curative or palliative, can be responsible for multiple physiologic changes. Indeed, localization of a tumour and its metastases and the effects of surgery, chemotherapy, and radiation therapy, in addition to comorbidities [diabetes, human immunodeficiency virus (HIV), etc.], as well as current medications, result in salivary alterations, modified anatomy, swallowing challenges, tooth decay, infections, etc.[3] Furthermore, as the oral cavity and its surroundings are implicated in important physiologic and social functions, even slight problems can generate dramatic consequences. Altered nutrition can delay recovery or exacerbate cachexia and compromise further treatment or precipitate agony. Anatomical changes can give rise to communication difficulties, disturb self-esteem, and alter social relations. In other words, mouth care is central to a patient's maintaining quality of life, which is clearly in accordance with the palliative care philosophy.

Question 2. Why is oral hygiene important in a palliative care context?

Understanding *why* mouth care is essential will help remember *how* it is best done. Depending on the level of care, illness progression, and the patient's preferences, the objectives can differ. Caregivers can aim for restoration, prevention, or comfort.[4] A patient's mouth is intimate; care should be taken to seek collaboration and consent during care. This still is true when a patient's level of consciousness is altered; for example, biting a sponge may be a way of refusing. As outlined in Question 1, primary and secondary complications of mouth problems are common and can potentially initiate a vicious cycle impacting quality of life. The mouth being at the crossroads of the digestive tract and the upper and lower respiratory systems, maintaining good function can facilitate eating, even when solely for pleasure and social interaction, and no longer for nutrition. Depending on the global situation, dental procedures can be indicated, either to restore function or to prevent further problems such as pain, infection, or even a loose tooth aspiration. Tackling halitosis can ease social contact. Preventing and treating a dry mouth will aid oral and inhaled medication intake. The most important point to stress about mouth care is the whole team should feel concerned, including the family and the patient. Whenever available, a dentist will be of great help.

Question 3. How should D.L. be advised on maintaining optimal oral hygiene?

Basic mouth care should include the entire area: lips, tongue, teeth, dentures, etc. Many recipes exist and will be adapted to available products and local practice. Table 17.1 lists the main mouth rinses and considerations for basic care. Remember plaque can form within 24 hours or less in a palliative patient.[1] Adjust the frequency to individual situations and preferences. Soft toothbrushes are recommended. Check for, and avoid, irritating ingredients in commercial preparations. Denture care, in addition to cleaning, may include remodelling when significant weight loss is present.

Case 17.1 (continued)

On day 22, D.L. presents to the outpatient oncology unit to receive his scheduled cisplatin. Upon questioning, it is found that he has Grade 2 mucositis, requiring a modified oral diet due to moderate pain.

Table 17.1 Basic oral care

Frequency	Ideally 3–4 times a day
Soft toothbrush	Include the tongue and dentures
Floss	Unless risk of bleeding
Lip balm	Avoid petroleum jelly content in patients under oxygen therapy (risk of ignition)
Mouth rinses	If commercial rinses or swabs are used, avoid glycerin or alcohol content (promotes xerosis)
Mouth rinse formulations	Saline water (NaCl 0.9%) or 2.5 ml table salt + 250 ml water
	Chlorhexidine gluconate 0.12%/0.05% cetylpyridinium chloride
	5 ml sodium bicarbonate 1.3% solution + 500 ml saline water (NaCl 0.9%)
	Hydrogen peroxide (H_2O_2) 3% solution in a 1:3 dilution with saline water (NaCl 0.9%)
	Best for crusts and hairy tongue
	Povidone–iodine (commercially available)
	Best for halitosis

Source: data from Martineau I, et al. 'Les soins de la bouche chez les malades en phase terminale'. Québec. Maison Michel-Sarrazin; 2008. P.561; and Fournier M-A, Beaulieu E. 'Soins de la bouche in Guide pratique des soins palliatifs'. 5th ed. Montréal. APES; 2019; p 205-222.3.

Question 4. How can mucositis be treated and how is the pain best managed?

Mucositis refers to mucosal damage caused by cancer therapy and can occur in the mouth, pharynx, larynx, oesophagus, and other areas of the gastrointestinal tract.[5] Stomatitis, on the other hand, refers to oral inflammation caused by infections, trauma, or medications. Chemotherapy and radiation therapy can cause mucositis and it is reported in up to 40% of patients receiving conventional doses of chemotherapy, 80% of patients undergoing chemotherapy as conditioning for haematopoietic stem cell transplantation, and almost everyone receiving chemoradiation of the head and neck.[5]

Mucositis manifests as erythematous lesions, with or without ulcerations, and can cause severe pain, which, in turn, can have a negative impact on cancer treatment dosing and oral intake, as well as on quality of life.[5] As good oral hygiene is important while undergoing cancer treatment, the general oral hygiene measures presented at the beginning of this chapter should be implemented before beginning cancer treatment. Other preventative measures can be implemented by the oncology team but are beyond the scope of this chapter.

Treatment for mucositis is mainly aimed at pain control in order to maintain adequate oral intake and quality of life. While many different mouthwashes (commercially available or compounded) have been described, only a few have been studied scientifically.[6] If the pain is not severe, pain control can be managed/approached with topical measures; otherwise, systemic pain control is more appropriate. Table 17.2 presents therapeutic options for mucositis caused by cancer therapy:[7,8]

Table 17.2 Therapeutic options for mucositis

Treatments	Comments
Systemic analgesia	◆ Transdermal fentanyl has been studied for mucositis due to conventional or high-dose chemotherapy with or without total body irradiation ◆ Patient-controlled analgesia with morphine has proven effective in patients undergoing haematopoietic stem cell transplantation ◆ Other systemic opioid chosen according to the clinical situation
Morphine 2% mouthwash	◆ Commercial product dosed at 1 mg/ml may be used as mouthwash to be swallowed or not
Doxepin 0.5% mouthwash	◆ Do not swallow
Lidocaine oral jelly 2%	◆ Rinse and spit every 4 hours as needed ◆ Risk of aspiration; do not eat or take other medications within 1 hours of using lidocaine ◆ Aerosol spray 10% can also be used; do not inhale or swallow
Ketamine 20 mg	◆ Commercially available product: 10 mg/ml or 50 mg/ml ◆ Rinse and spit every 3 hours as needed ◆ Can be further diluted in artificial saliva or another liquid extemporaneously as needed ◆ Case reports suggest that ketamine is an effective mucositis pain reliever ◆ Do not swallow, as it could have a systemic effect and cause adverse events
Sucralfate mouthwash 1 g/5 ml	◆ While often mentioned as a potential treatment, it is NOT recommended by most experts to prevent nor treat mucositis as its efficacy has not been demonstrated and due to its high sugar content ◆ Reported to be effective in relieving oral irritation
'Magic' mouthwash	◆ Many different mouthwash formulae exist, each containing a variety of ingredients, the most common being an antacid, diphenhydramine, nystatin, steroids, and lidocaine ◆ Few recipes have been studied and compared to each other and to commercial products ◆ One trial found lidocaine, antacid, and diphenhydramine mouthwashes to be better than placebo at pain control ◆ It is not recommended to use Magic mouthwash to treat thrush ◆ Avoid preparations containing tetracycline, as they favour bacterial resistance

Sources: data from Lalla RV, et al. 'MASCC/ISOO Clinical Practice Guidelines for the Management of Mucositis Secondary to Cancer Therapy'. Cancer. 2014; 1453–615; Mc Guire DB. 'Mucosal tissue injury in cancer therapy. More than mucositis and mouthwash'. Cancer Pract. 2002; 10(4):179–91.7; and Miller RC, Le-Radermacher J, Sio TT et al. 'A Phase III, Randomized, Double-Blind Study of Doxepin Rinse versus Magic Mouthwash versus Placebo in the Treatment of Acute Mucositis Pain in Patients Receiving Head and Neck Radiotherapy with or without Chemotherapy' (AllianceA221304). Int J Radiat Oncol Biol Phys. 2016;938. 8

Case 17.1 (continued)

D.L. is offered a doxepin rinse to better control his pain and to try to maintain oral intake.

On day 43, he presents to the outpatient oncology clinic to receive his last cisplatin dose. He complains of white patches all over the mouth and discomfort. Upon examination, he is found to have oral candidiasis.

Question 5. What would be the optimal management of D.L.'s oral infection?

Most oral infections are of fungal or viral origin, caused by either *Candida albicans* or herpes simplex virus. Some factors may predispose patients to these conditions such as a reduction of salivary flow caused by drugs, radiation treatment or surgery, prosthetic material, inadequate mouth hygiene, or malnutrition.[9]

Oral candidiasis manifests usually as white lesions. The most common form pseudomembranous candidiasis, commonly known as 'oral thrush', manifests as confluent white plaques that can be wiped off with gauze, leaving an erythematous surface below. Another white form of candidiasis is the hyperplastic form, in which the white plaques cannot be wiped off. Candidiasis can also present as red erythematous lesions like in acute or chronic atrophic candidiasis or in the angular cheilitis form.[9] One of the first choices to treat oral candidiasis is topical nystatin. Other topical treatments include clotrimazole or chlorhexidine. If the infection does not respond to topical therapy or is more invasive, systemic treatment with fluconazole or itraconazole can be given.[3,9,10,11] It is also important to emphasize basic oral hygiene measures as they can prevent relapses.[11]

Herpes simplex oral infection manifests as erythematous vesicular lesions. In immunocompromised patients, it can be more extensive and aggressive. It often coexists with oral mucositis, making the diagnosis more challenging. A swab of the lesion can be taken to confirm it. Topical treatments are usually reserved for immunocompetent patients with recurrent herpes labialis, as it is most effective if applied before the onset of vesicles.[12] Table 17.3 lists common treatments, dosages, and durations for oral infections.

Case 17.1 (continued)

D.L. is prescribed nystatin 500 000 units to gargle four times a day. One week later, he comes back for follow-up and still complains of white patches. He also has little oozing with blood. The mucositis is still present as radiation therapy continued but now presents with light oral bleeding.

Question 6. How can D.L.'s mucosal bleeding be managed?

In cancer patients who are thrombocytopenic secondary to chemotherapy, local intraoral bleeding can coexist with mucositis. Usually, it can be managed with topical haemostatic agents such as gelatin sponge or gentle pressure with sterile gauze. If bleeding is not controlled, a tranexamic acid 4.8% rinse can be offered at a dosage of 10 ml four times a day. It is also important to continue basic oral care, as gingivitis can increase the risk of gingival bleeding.[1,13]

Case 17.1 (continued)

As D.L.'s oral candidiasis is not controlled with nystatin, a 7-day course of fluconazole 100 mg po daily was offered, in conjunction with tranexamic acid rinses, until bleeding stops.

He is seen for a follow-up appointment 4 months after the end of his chemoradiation and complains of severe xerostomia.

Table 17.3 Treatments for oral infections

Drug	Dosage and duration	Note
Oral candidiasis treatment		
Nystatin suspension	500 000–1 000 000 units topically four times a day for 14 days or more	Can be swallowed. Wait 30 minutes before eating or drinking as acts as local agent
Clotrimazole 1% cream	Apply 2–3 times a day for 3–4 weeks	
Chlorhexidine 0.12% solution	15 ml three times a day	Can modify taste
Fluconazole tablets	150 mg po x 1 dose OR 100 mg po daily for 7–14 days	Needs to be adjusted in renal insufficiency
Itraconazole capsules	200 mg po daily for 7–14 days	
Oral herpes simplex treatment		
Topical acyclovir 5%	Apply six times a day for 7 days	Combination with topical corticosteroid can lower recurrences and pain, and accelerate healing of ulcers
Docosanol 10%	Apply five times a day complete healing	Lowers the healing time of approximately 18 hours and lowers pain
Acyclovir tablets	400 mg po three times a day for 7–10 days (can also be given intravenously if invasive disease)	Dose may need to be adapted to renal function
Valacyclovir tablets	2000 mg po twice a day for two doses given with first signs or symptoms (in immunocompetent patient) 1000 mg po twice a day for 7–10 days	
Famciclovir tablets	250 mg po three times a day for 7–10 days	

Sources : data from Fournier M-A, Beaulieu E. 'Soins de la bouche in Guide pratique des soins palliatifs'. 5th ed. Montréal. APES; 2019; p 205–222.3; Millsop JW and Fazel N. 'Oral candidiasis'. Clinics in dermatology. 2016;(34):487–494. 9; Lagman R, et al. 'Single-dose fluconazole therapy for oral thrush in hospice and palliative medicine patients'. Am J Hosp Palliat Care. 2016; (33).10; and Arduino PG and Porter SR. 'Oral and perioral herpes simplex virus type I (HSV-1) infection: review of its management'. Oral Diseases. 2006;(12):254–270. 12

Question 7. How can D.L.'s xerostomia be managed?

Xerostomia is a sensation of dryness in the mouth. It can be caused by a decrease in the volume of saliva secreted by the salivary glands or by a change in saliva composition.[14] Xerostomia is a frequent complication in cancer patients, especially for those undergoing head and neck radiation therapy. It can be caused either by the destruction of salivary glands by radiation or tumour infiltration or by numerous medications, including anticholinergics, diuretics, opioids, antidepressants, antipsychotics, antihistamines, etc. It can lead to several complications, including oral discomfort, taste disturbance, difficulty in chewing or swallowing, halitosis, oral candidiasis, dental caries and erosion, and psychosocial problems such as anxiety and social isolation.[14]

Table 17.4 Commonly used products for xerostomia

Product or measure	Note
Basic mouth hygiene Increase oral hydration Chew ice chips, iced-juice chips, non-sugar chewing gum, or candies Fresh fruits	Avoid salty or sugary foods Avoid alcohol and caffeinated drinks
Salivary substitutes	Can be used as often as needed. Contain sorbitol or xylitol, which are non-absorbable sugars that can cause diarrhoea in sensitive patients if used in excessive amount
Xylitol (available in gums, tablets, adhesive tablets, mouthwash)	Non-absorbable sugar that stimulates salivation Can cause diarrhoea if used in excessive amount in sensitive patients. It is best to advise starting in low dose and increase if needed as tolerated
Anethole trithione: 25 mg po 2–3 times a day	Increases the cholinergic muscarinic receptor number—needing a salivary residual function
Pilocarpine 2.5–5 mg po 3–4 times a day (can use eye drops under the tongue instead, less expensive)	Stimulates cholinergic receptors

Source: data from Fournier M-A, Beaulieu E. 'Soins de la bouche in Guide pratique des soins palliatifs'. 5th ed. Montréal. APES; 2019; p 205–222.3

In order to manage D.L.'s xerostomia, the first thing that should be done is to review his medication list to search for known medications that can cause xerostomia. If possible, cessation of the relevant drug(s) can help or prescribing an alternative drug causing less xerostomia is advised.

In addition, he should be advised to maintain good oral hygiene and to consider salivary substitutes and saliva-stimulant drugs. Table 17.4 presents commonly used products.

References

1. **Martineau I, Faucher T, Levesque S, Moreau J** (2008) *Les soins de la bouche chez les malades en phase terminale.* Maison Michel-Sarrazin, Québec.
2. **Nakajima N** (2017) Characteristics of oral problems and effects of oral care in terminally ill patients with cancer. *Am J Hospice Palliat Med*, **34**(5), 430–4.
3. **Fournier M-A, Beaulieu E** (2019) Soins de la bouche. In: editors (eds.) *Guide Pratique des Soins Palliatifs*, 5th edn, pp. 205–22. APES, Montréal.
4. **Treister NS, Villa A, Thompson L** (2020) *Palliative care: overview of mouth care at the end of life*. https://www.uptodate.com
5. **Lalla RV, Bowen J, Barasch A** *et al.* (2014) MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*, **120**(10), 1453–61.
6. **McGuire DB** (2002) Mucosal tissue injury in cancer therapy. More than mucositis and mouthwash. *Cancer Pract.* **10**(4), 179–91.
7. **Miller RC, Le Radermacher J, Sio TT** *et al.* (2016) A phase III, randomized, double-blind study of doxepin rinse versus magic mouthwash versus placebo in the treatment of acute mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy (AllianceA221304). *Int J Radiat Oncol Biol Phys*, **96**, 938.

8. **Cerchietti LC, Navigante AH, Bonomi MR** *et al.* (2002) Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. *Cancer*, **95**, 2230–6.
9. **Millsop JW**, **Fazel N** (2016) Oral candidiasis. *Clin Dermatol*, **34**, 487–94.
10. **Lagman R, Davis M, LeGrand S** *et al.* (2016) Single-dose fluconazole therapy for oral thrush in hospice and palliative medicine patients. *Am J Hosp Palliat Care*, **34**, 645–9.
11. **Gomes Carvalho C, Medeiros-Filho JB**, **Coelho Ferreira M** (2018) Guide for health professionals addressing oral care for individuals in oncological treatment based on scientific evidence. *Support Care Cancer*, **26**, 2651–61.
12. **Arduino PG**, **Porter SR** (2006) Oral and perioral herpes simplex virus type I (HSV-1) infection: review of its management. *Oral Dis*, **12**, 254–70.
13. **Lalla RV, Sonis ST**, **Peterson DE** (2008) Management of oral mucositis in patients with cancer. *Dent Clin North Am*, **52**(1), 61–viii.
14. **Davies A, Bagg J, Laverty D** *et al.* (2010) Salivary gland dysfunction ('dry mouth') in patients with cancer: a consensus statement. *Eur J Cancer Care*, **19**, 172–7.

Chapter 18

Lymphoedema

Anna Towers and Marie-Ève Letellier

Attitude

To enable each learner to:

- Reflect on the importance of prevention, early diagnosis, and referral, of a multidisciplinary approach, and of long-term follow-up in the care of lymphoedema patients.
- Consider patients who may be socially or financially impacted by lymphoedema.

Skills

To enable each learner to:

- Understand the links between lymphoedema and chronic oedema.
- Demonstrate an initial clinical assessment and referral.
- Guide the patient on self-help measures.
- Empathize with the patient and family who are impacted by lymphoedema.
- Work in concert with a specialty lymphoedema team, and advocate for the establishment of appropriate multidisciplinary services if these are not available.

Knowledge

To enable each learner to:

- Identify the common causes of lymphoedema.
- Describe the common symptoms and psychosocial concerns experienced by the patient.
- Describe the elements of decongestive lymphatic therapy (DLT) for lymphoedema.
- Recognize the availability of surgical interventions.
- Describe how decongestive therapies need to be adapted in the context of advanced cancer.

Case 18.1

V.P. is a 54-year-old ward nurse who was diagnosed 5 years ago with Stage II adenocarcinoma in the right breast, which was treated with lumpectomy, axillary node dissection, radiotherapy, and adjuvant chemotherapy. V.P. is married, with a grown daughter who lives nearby with her family. Three months ago, she began to notice swelling of her right arm. One month ago, it spread to her hand. She is worried that her cancer might have returned. She knows that lymphoedema is treated with a sleeve and glove and she cannot see herself working as a ward nurse while wearing such garments. The swelling does not go away completely overnight or with elevation.

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On examination, she has mild oedema of her right breast and moderate oedema of her right arm and hand pitting. There is a 3 cm difference in circumference of the arms at the elbow. There is no redness, warmth, or tenderness.

Question 1. What is lymphoedema and what is the aetiology of V.P.'s lymphoedema?

Lymphoedema is a chronic inflammatory condition caused by damage to the lymph vessels or nodes, by long-standing overload of the lymphatic transport system, or a malformation of lymph vessels[1,2,3,4,5] (see Table 18.1).

There is a protein-rich accumulation in the interstitial space due to reduced lymph transport capacity.[1,2,3] The chronic inflammatory complications are especially evident when the lower limbs are involved.

The lymphatic vascular system (LVS) is a network of vessels just as elaborate as the blood circulatory system. The main function of the LVS is to transport interstitial fluid and proteins back to the venous circulation.[1,2,3,4] Almost all of the fluid that escapes from the arterial circulation (at least 4 litres per day) is returned to the heart via the lymphatic system.

Chronic lymphoedema is a failure of the LVS. The increased protein (and therefore increased colloid osmotic pressure of the interstitial fluid) leads to an influx of fluid from the plasma, setting up a vicious cycle of high-protein oedema.[1,2,3,4] The more general term *oedema* refers to excessive fluid in the body tissues, vascular space, and within cells, of varied aetiology. Any chronic oedema, however, will overload the lymphatic transport system and eventually lead to lymphatic vessel damage or lymphoedema.

Lymphoedema most commonly occurs in the limbs but can occur in any part of the body. If untreated, the chronic inflammatory state of the tissues leads to marked fibrosis and abnormal fat deposition.[2,4] Skin changes occur in the form of papillomatosis (hypertrophy of dermal papillae), pachydermia ('elephant skin'), thickened skinfolds, hyperpigmentation, and inflammatory dermatoses.[1,2,3,5] Although lymphoedema itself is usually painless, there is eventual fibrosclerosis with enclosure of vessels and nerves that can cause pain. Most importantly, lymphoedema/chronic oedema is the most common cause of bacterial infections of the skin and subcutaneous tissues (cellulitis, erysipelas).[1,2,3,4,5] Each episode of cellulitis further destroys the very delicate lymphatic

Table 18.1 Aetiology of lymphoedema

	Primary lymphoedema	**Secondary lymphoedema**		
Cause	Malformation of lymph vessels or nodes	Trauma	Chronic overload	Malignant: active tumour affecting nearby lymphatic vessels or nodes
Examples	Congenital, present at birth	Cancer treatment	Obesity	Primary tumour
	Manifest in childhood or early adulthood	Other surgeries	Chronic venous insufficiency	
	Manifest later in life	Accidents	Long-standing immobility	Cancer recurrence
	As part of syndromes (e.g. Klippel–Trenaunay)	Filariasis		

vessels and makes the lymphoedema worse. Other complications include interdigital and nail mycosis, lymph cysts and fistulae, macerated skin, and lymphorrhoea.[1,2,3] Untreated lymphoedema may become so severe that the limb becomes functionally useless.[5]

The most common causes of lymphoedema in the developed world are morbid obesity, chronic venous insufficiency, cancer treatment, and other multiple surgeries.[4,6,7] Cancer surgery (axillary or inguinal node dissection) or radiotherapy can damage lymph vessels and nodes. Overall, the incidence of lymphoedema following breast cancer treatment is reported as 20–30%.[5] More extensive surgical procedures and radiotherapy increase the risk. Sentinel node biopsy, when performed alone, is associated with a lower risk.[5] Other cancers often associated with lymphoedema are: melanoma (incidence rates 1–66%), gynaecological cancers (5–73% incidence), prostate cancer (1–18% incidence), and sarcoma (6–30% incidence).[3,5]

V.P.'s arm lymphoedema is related to the axillary node dissection and radiotherapy that she underwent. There is often a latency period of 2–3 years or longer from the time of cancer treatment to the manifestation of oedema. The latency period is thought to be due to progressive fibrosis.[2,4]

Question 2. When a patient presents with a new onset of oedema, what important conditions must be ruled out in the medical assessment?

Since the onset of lymphoedema may signal the recurrence of cancer, it is essential that the treating physician consider this possibility. Other causes of oedema can include deep venous thrombosis (DVT) or cellulitis. A Doppler ultrasound or impedance plethysmograph is indicated if you suspect a DVT. If cellulitis is present, a complete blood count may reveal an elevated white blood count and an increased number of neutrophils (if the immune system is intact). A computed tomography (CT) scan of the chest might show an apical tumour that could be obstructing lymph flow. A CT scan of the brachial plexus may also be indicated to exclude a recurrent tumour.

Case 18.1 (continued)

You order a complete blood count and CT scans of the chest and brachial plexus, which are normal. Since the arm and hand oedema is more than minimal and there is pitting present, you refer her to a lymphoedema specialist for DLT.

Question 3. Who are the usual members of a specialty lymphoedema team?

Members of a specialty lymphoedema team have specific training in physical therapies for lymphoedema.[1] These teams are often interdisciplinary and may include allied health care professional(s) and a physician. Some communities may not have access to such a team but may have solo lymphoedema practitioners who will be able to administer DLT.

Question 4. What are the elements of decongestive lymphatic therapy?

Decongestive lymphatic therapy (DLT) is the standard therapy for lymphoedema[2,3,5] and has five pillars: (1) manual lymphatic drainage (MLD); (2) compression; (3) skin care; (4) exercises; and

(5) self-management. It aims to improve lymphatic drainage through existing lymphatics and to encourage collateral circulation. There are two phases to this treatment: an intensive phase to reduce the size of the limb by eliminating any pitting oedema—generally lasting 2–4 weeks, but occasionally longer; and a lifelong maintenance phase with compression and self-management to maintain the reduction. The patient may benefit from further intensive treatment over time to achieve and maintain the minimum oedema volume.[1,2,3]

Mild Stage I lymphoedema that reverses spontaneously with elevation may be treated directly with compression garments (maintenance phase).[1] A more marked Stage II lymphoedema, which does not reverse with elevation (evidence of fibrosis), is managed with an initial period of intensive treatment that includes bandaging. Stage III lymphoedema, in which skin changes are present,[1] is also managed with intensive treatment.

The five pillars of DLT

1. *MLD*. The aim of this specific massage is to increase the intrinsic contractility of the superficial lymph vessels and thus improve lymph flow.[2,3] Unskilled and overly vigorous massage is counterproductive since it may increase blood flow or cause lymphangiospasm. Patients, or relatives, can often be taught a simplified version of the massage known as simple lymphatic drainage (SLD).[3] MLD has been shown to do no harm and to be useful in situations where compression solutions might be limited such as in head and neck or truncal oedema. However, there is no consensus on its effectiveness if used alone.[1]
2. *Compression bandaging*. Compression is the key therapy element. Specific low-stretch inelastic bandages are applied daily and kept on for 24 hours.[2,3] Bandages are removed at the time of the next daily treatment and re-applied after skin care and MLD. Elastic 'ACE'-type or 'tensor' bandages are not appropriate for lymphoedema management because they exert high resting pressure and may be uncomfortable when applied over a whole limb. Once limb reduction is achieved, 24-hour bandaging is continued while waiting for delivery of a custom-made garment that is worn during the day. A minority of patients continue to require compression at night to control the swelling. The reduction treatment works best if the oedema is still soft and pitting, hence the importance of early diagnosis and treatment before irreversible fibrosis develops.[5]
3. *Elastic sleeves/stockings (compression garments)*. Compression garments are the cornerstone of lymphoedema management and, except for mild lymphoedema, should be prescribed only after oedema reduction with intensive therapy.[1,5] Where deepened skinfolds are present, it is especially important to reduce the oedema before prescribing a compression garment; otherwise, a counterproductive tourniquet effect could occur. In palliative cases where oedema can vary from day to day, garment wear may not be possible and other components of treatment must be adapted to each specific case.[2,8]
4. *Exercise.* Specific daily exercise is an integral part of DLT. Lymphoedema is often associated with muscle atrophy and weight gain. Exercise that rebuilds muscles will help reduce the oedema and aerobic exercise will help with weight control.[3] In addition, there are a myriad of general and specific exercises for lymphoedema, ranging from low intensity (e.g. yoga, tai chi, aquatic therapy) to high intensity (e.g. dragon boat racing).[1] None have led to adverse events as regards the onset or progression of lymphoedema.[1,9] Aquatic therapy/water-based exercise programmes are especially interesting due to the natural compression of water when exercising and they may help improve skin condition. Not all patients (particularly those with wounds or skin issues) are candidates for aquatic therapy.[1] Any type of exercise should start progressively with low to moderate intensity. Theoretically, overly vigorous exertion that increases blood flow could temporarily increase oedema.

5. *Sequential pneumatic compression pumps*. Pneumatic compression machines are occasionally used. Inflatable multi-chambered sleeves applied to the limb mechanically squeeze the soft tissues to passively move lymphatic fluid to the drainage points in the limb. Pumps may be used in conjunction with DLT or compression hosiery.[1,2] A theoretical limitation of mechanical pumps for cancer-related lymphoedema is that they may simply push fluid into truncal areas (or the genitals, in the case of lower limb oedema).[1]

Question 6. How does compression therapy work?

Compression enhances external stimulation from exercise (striated muscle effect) that enables lymphatic flow.[2,3] External compression will also increase interstitial pressure and reduce the pressure gradient that forces fluid out of the capillaries, thus reducing fluid fluxes into the interstitial space. Compression on a limb will thus prevent fluid accumulation.[2,8] Multiple layers of inelastic bandages with low extensibility produce high working pressures that, with movement, create a massaging effect, stimulating lymph flow. At rest, the pressure is constant and non-stimulating. Compression garments work similarly and must be well fitted by appropriately trained practitioners.[2,8]

Question 7. What are the contraindications and cautions regarding compression therapy?

In the intensive oedema treatment phase, compression increases venous return to the heart and therefore, congestive heart failure may be worsened. Diuretics may therefore need to be increased during intensive DLT. In the acute stages of DVT, the limb may not tolerate either stockings or bandages. However, light compression (but not MLD) could be resumed once the patient is adequately anticoagulated. Caution always needs to be used in the case of arterial insufficiency and peripheral neuropathy.[2,3,8] This is especially relevant for lymphoedema of the legs.

Case 18.1 (continued)

V.P. returns for a second visit, at which time she continues to express distress at her condition. In addition to arm swelling, she has been having shooting pains in her arm since her surgery. The combination of pain and swelling has begun to impact many aspects of her home and work life. Her spouse now tends to do the shopping, vacuuming, and heavy cleaning. V.P. finds that standard clothing no longer fits. She is afraid of implications for her work at the hospital. She feels overwhelmed and discouraged.

Question 8. What psychosocial considerations are relevant to the assessment and care of V.P.?

A lymphoedematous limb may be a constant reminder of cancer that is impossible to conceal. It requires lifelong management, and it may be difficult for a cancer patient who is in remission to accept this.[1] V.P. has expressed concern that the oedema could get worse and prevent her from working. Lymphoedema, pain, and disabilities of shoulder, arm, and hand function are frequent sequelae of breast cancer treatment that can negatively impact work, family, sexual, and social life.[5] Evaluation of these physical problems and for possible depression is indicated.

Case 18.1 (continued)

You assess V.P. for clinical depression. She does not fit published criteria. You offer her support and reassure her that you will advocate for her in explaining her condition to her hospital employer. You will support her if she needs a job reassignment. You refer her to a physiotherapist familiar with arm and shoulder dysfunction following cancer treatment. You start to educate her concerning self-care and treatment options, and offer to see her with her spouse in order to enlist their participation in a lifelong maintenance programme.

Question 9. What advice would you give V.P. about self-care to prevent worsening of her condition?

It is important, both physically and psychologically, that V.P. continues to lead as active a life as possible. Skin hygiene, similar to that practised by diabetic patients, is essential to prevent cellulitis, injury, and further lymphatic decompensation.[1] Regular cleansing and use of a non-allergenic moisturizing cream are indicated. The patient should prevent trauma and punctures to the skin. She should avoid extremes of heat (saunas, hot packs, sunburn) that can cause hyperaemia or impact skin integrity.[1,10]

Long-haul airplane flights, if there is reduced cabin pressure, might exacerbate lymphoedema. Patients with confirmed lymphoedema should wear a well-fitted compression garment, and those at risk of lymphoedema should be informed of this.[10]

Obesity makes lymphoedema worse. Therefore, achieving and maintaining a healthy body weight and exercising regularly are important.[1,2,3] V.P. will want to assess her diet and find what exercise is best for her.

Question 10. What are the treatment options for V.P. at this time?

Once the patient has completed the intensive treatment phase, the physician should order a medical compression garment.[1,3] The lymphoedema therapist could give guidance regarding the level of compression (typically either 20–30 mmHg or 30–40 mmHg for arm lymphoedema). Custom-made flat-knit garments are best as they breathe more freely and are designed to fit the contours of the limb and so avoid tourniquet effects that worsen oedema. If the oedema is mild and there are issues of cost, or of cosmetic appearance, off-the-shelf standard circular-knit garments might be suitable.[1,3]

Lymphoedema is like any other chronic medical condition where daily care and regular medical follow-up are important. All patients should receive coordinated healthcare tailored to their needs.

Question 11. Are any medications helpful for lymphoedema?

Diuretics are not a good choice to treat lymphoedema.[1,2] Diuretics reduce the volume of lymphoedematous tissue by haemoconcentration. Stagnating plasma proteins remain in the tissues and trigger fibrosis and infection. One should avoid long-term use of diuretics, although they may be useful where there is a cardiac or venous component to the oedema, and in palliative cases where there is severe mixed oedema and prognosis is short. Some medications can make oedema worse, including non-steroidal anti-inflammatory drugs (NSAIDs), calcium antagonists, and alpha blockers.[2]

Currently, there are no proven effective pharmacological agents to treat lymphoedema.[2] Animal investigations into promising molecular targets are under way.[1,2]

Question 12. What surgical techniques are effective for lymphoedema?

When conservative treatments fail, there are two main categories of surgical treatment for lymphoedema: (1) surgical reduction (debulking or liposuction); and (2) restoration of lymph flow through lymphaticovenous anastomoses or lymph node transfer.[1,2,5,7] Liposuction aims to reduce the excessive abnormal fat and often requires lifelong 24-hour use of compression garments subsequently.[1] Lymphaticovenous anastomoses involves microsurgical regrafting and may give better results when employed in earlier stages of lymphoedema. Investigations are ongoing to determine the indications and outcomes for each of these surgical techniques.[7]

Case 18.2

S.M. is a 57-year-old married woman with a recent diagnosis of Stage 4 ovarian cancer, peritoneal and retroperitoneal metastases, and bilateral leg oedema (left > right). She is still being assessed for possible chemotherapy. Four months ago, she noticed painless swelling in her legs. She was assessed for DVT at that time and ultrasound scans were negative. She is now admitted because of nausea and vomiting, due to a partial small bowel obstruction which is resolving with conservative medical management. She has become less mobile in the past few months, spending most of her time either in a chair or in bed. You are the physician assessing her, and she expresses concern regarding her leg swelling. On examination, she has marked pitting oedema of the entire left leg and some oedema of the suprapubic area and right upper leg. Haemoglobin is low at 10.5 g/dl (normal 12–16), and albumin is low at 26 g/l (normal 35–52). Creatinine and renal function are normal.

Question 13. What are the possible causes of S.M.'s oedema?

In palliative patients with recurrent cancer, lymphoedema of varied aetiology often coexists; S.M.'s oedema is probably multifactorial.[8] The asymmetry and proximal oedema point to lymphatic transport system obstruction as a component. Venous obstruction related to the intra-abdominal and pelvic tumours should be considered; however, CT scanning showed no thrombosis. A factor in this patient is her immobility (lack of muscle pump that aids both venous and lymphatic circulation). Hypoalbuminaemia is another common contributor to oedema in advanced cancer. Liver metastases may lead to portal venous hypertension, ascites, and leg oedema. Congestive heart failure causes peripheral leg oedema but is probably not a cause in this case.

Question 14. What would be the goals of treatment in this palliative case? What physical treatment options are there?

Oncologic treatment is key, if this is still possible. Anything that reduces tumour burden will improve malignant lymphoedema.[11] Improved quality of life and relief of symptoms are also important goals—to reduce swelling (or at least to prevent it from getting worse); to improve

mobility; to prevent lymphorrhoea or skin oozing (which is distressing to patients and makes nursing care difficult); and to prevent skin and subcutaneous infections.[11] Skin care, good hygiene, and early diagnosis and treatment of bacterial or fungal infections are important. Any open wounds will need specific nursing care. Compression bandaging or devices can be applied over wound care products.

In palliative patients, compression stockings (even custom-made flat-knit garments) are often not well tolerated. The day-to-day variable nature of the oedema may render stockings too tight, difficult to apply, and possibly productive of a tourniquet effect.[8] However, multilayer inelastic bandages using lower pressures usually help reduce the swelling and control lymphorrhoea.[1,8,11] Soft padding under the compression bandages will prevent skin damage over bony prominences. Commercially available Velcro-type compression devices may replace bandages in this context, being easier to don and doff.[1] Any coexisting pain or other symptom that impairs mobility should be meticulously treated.[11,12]

Gentle active exercise should be encouraged. If there is no contraindication, MLD massage may also help lymphatic flow and provide comfort and human touch in a difficult situation. Nutritional support may help improve function and maintain skin integrity. Management of bowel and bladder functions may need specific consideration, especially when bandaging systems are used.

Subcutaneous needle drainage techniques ('reverse hypodermoclysis') have been employed to treat massive oedema in palliative cases, and successes have been reported.[11,12] Cellulitis risk and albumin loss are concerns.

Communication with patient and family is important to maximize collaboration with treatment. Financial concerns may need to be addressed if lymphoedema treatments and appliances are not fully covered.

Case 18.2 (continued)

The physician consults a therapist trained in lymphoedema management who applies a compression bandage system on the left leg. This is removed and re-applied daily. The therapist enlists the help of palliative nurses to re-bandage the leg on days when she cannot attend. The oedema reduces significantly over a two-week period and a Velcro-type compression aid is obtained to use 24 hours per day to maintain reduction of the left leg. The team monitors the oedema of the other leg.

Question 15. What medications might help reduce oedema in the situation of advanced malignancy?

S.M. could be encouraged to pursue any appropriate oncological treatments that may reduce the tumour masses impeding lymphatic flow. Dexamethasone may reduce peri-tumoral oedema and, potentially, tumour size. However, corticosteroids may also cause oedema.[11,12] High-dose diuretics may produce short-term positive effects in palliative patients, but one would need to monitor for metabolic complications.

Case 18.2 (continued)

S.M. is discharged from hospital and her family is able to manage the oedema, with the support of twice-monthly visits to the lymphoedema therapist. She dies 6 months later of complications related to malignant bowel obstruction. However, her leg oedema had remained controlled, and her skin intact.

Future trends

Greater awareness on the part of physicians and health professionals will enable early diagnosis and treatment of lymphoedema with compression therapy. In particular, those with non-cancer causes of lymphoedema, such as obesity and venous disease, are underdiagnosed and undertreated. Early intervention will help minimize the morbidity and mortality related to lymphoedema and chronic oedema—in particular, the problems of wounds, recurrent cellulitis and death from sepsis.

More conservative cancer surgery and radiotherapy regimes are causing a downward trend in the incidence of cancer-related lymphoedema. However, lymphoedema is still a significant problem as patients are surviving longer and lymphoedema can develop years after cancer treatment.

Advocacy is needed to ensure that lymphoedema treatments are accessible to all who need them. Health professionals can take a leadership role to improve the care of these patients.

References

1. **Executive Committee** (2016) The diagnosis and treatment of peripheral lymphedema: 2016 Consensus Document of the International Society of Lymphology. *Lymphology*, **49**(4), 170–84.
2. **Lee B-B**, **Rockson SG, Bergan J** (2018) *Lymphedema: A Concise Compendium of Theory and Practice*. Springer, Cham.
3. **Zuther JE**, **Norton S** (2017) *Lymphedema Management: The Comprehensive Guide for Practitioners*. Thieme, New York, NY.
4. **Breslin JW, Yang Y, Scallan JP, Sweat RS, Adderley SP, Murfee WL** (2019) Lymphatic vessel network structure and physiology. *J Comp Physiol*, **9**, 207–99.
5. **Shaitelman SF, Cromwell KD, Rasmussen JC** *et al.* (2015) Recent progress in the treatment and prevention of cancer-related lymphedema. *CA Cancer J Clin*, **65**(1), 55–81.
6. **Keast D, Towers A** (2017) The rising prevalence of lymphedema in Canada: a continuing dialogue—accurately estimating lymphedema rates in Canada is not easy. Lymphedemapathways.ca, Spring, 5–8.
7. **Carl HM, Walia G, Bello R** *et al.* (2017) Systematic review of the surgical treatment of extremity lymphedema. *J Reconstr Microsurg*, **33**(6), 412–25.
8. **Moffatt C, Partsch H, Schuren J** *et al.* (2012) *Compression therapy. A position document on compression bandaging*. **International Lymphoedema Framework**.
9. **Stout NL, Baima J, Swisher AK, Winters-Stone KM, Welsh J** (2017) A systematic review of exercise systematic reviews in the cancer literature (2005–2017). *PM R*, **9**(9), S347–84.
10. **Asdourian MS, Skolny MN, Brunelle C, Seward CE, Salama L, Taghian AG** (2016) Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis. *Lancet Oncol*, **17**(9), e392–405.
11. **International Lymphoedema Framework**, **Canadian Lymphedema Framework** (2010) *The management of lymphoedema in advanced cancer and edema at the end of life.* Position document. https://www.lympho.org/wp-content/uploads/2016/03/Palliative-Document.pdf
12. **Towers A, Hodgson P, Shay C, Keeley V** (2010) Care of palliative patients with cancer-related lymphoedema. *J Lymphoedema*, **5**(1), 72–80.

Chapter 19

The last days and hours

David Henderson and Leonie M. Herx

Attitude

To enable each learner to:

- Reflect on what it means to plan for an expected death.
- Realize the importance of education, planning, and guidance for the patient, family, and care team to understand when death is near.
- Reflect on the importance of self-awareness and how one's own attitudes towards death and dying may affect the care provided.

Skills

To enable each learner to:

- Recognize a patient's and family's wishes for an expected death in various locations, including their home.
- Assess and evaluate the ability to have a home death, including risks and benefits.
- Develop a care plan for the dying patient and their family and identify potential gaps in resources for that plan.
- Recognize when death is near and prepare the patient and family for this.

Knowledge

To enable each learner to:

- Describe the signs and symptoms of imminent death.
- Describe the consequences of home or hospital death without an effective plan and resources in place.
- Describe situations when to call a medical examiner/coroner.

Case 19.1

H.H. is a 72-year-old woman with Stage 4 lung cancer, living with her husband, one adult child, and two grandchildren aged 10 and 13. H.H.'s condition has been changing and she recognizes her life is winding down. Her disease has progressed despite chemotherapy and immunotherapy. No additional treatments for her cancer are being offered. Her Palliative Performance Scale (PPS) is now 40% and has been dropping quickly, having been 60% 3 weeks before. A discussion about advance care planning (ACP) with her family physician was held about 3 months ago, while she was still on palliative chemotherapy. She and her husband and daughter have had additional discussions over the last month about her final wishes. H.H. and

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her husband want to be cremated and do not want to be a bother to the family, so were not going to have a memorial or funeral service. She wants to speak with her family physician further about her end-of-life care wishes.

Question 1. Is there a role for healthcare professionals to discuss end-of-life rituals?

Dr Alan Wolfelt has described the importance of end-of-life rituals in the grieving process, for both the individual and their family, and how our society has moved away from these processes.[1] Asking about personal wishes is important to patients and families to feel that we, as healthcare professionals, care about them as people, and not just illnesses. These discussions are best had long before they enter the last days and hours of life, so we can understand how best to support them and develop a plan for end-of-life care.[1]

Case 19.1 (continued)

The family physician initiated a discussion with H.H. regarding potential supports for her and her family regarding end-of-life care. The physician spoke to her about the value of having a structured way for her family and friends to grieve together as a family after her death. H.H. also expressed worry about her grandchildren, so the physician gave them information about Canadian Virtual Hospice and, in particular, their section on children's grief.[2] The doctor felt it would assist the grandchildren by helping them learn how to grieve as part of a supportive family. The family physician also suggested they sit down as a family and discuss her ACP and goals of care. H.H. is considering her options of staying at home or being admitted to hospital or hospice towards the end of her life.

Question 2. What needs to be considered in managing the last days and hours of life before discussing a potential home death with a patient and family?

Before we begin a discussion about a possible home death, it is prudent to consider some factors that may impact its practicality and success for an individual patient and their family. Firstly, we need to consider the course of the underlying illness leading to the person's impending death and what burden of symptoms they might encounter as dying unfolds. Can these symptoms be managed adequately in a home environment with the resources available? Do the patient and family understand the current condition, future path, and expected timeline until death? Does the patient have an ACP and/or have they expressed their goals of care? Is there a substitute decision-maker (SDM) identified and has the SDM been involved in the ACP/goals of care discussion?

We also need to understand a family's previous experiences with death and dying, and what their fears and worries might be. We know that how a family perceives a death to go, good or bad, can have a lifelong effect on how they will anticipate deaths of other people close to them and their own death. If prior death experiences have gone well and they were well supported, the fear of dying will be diminished. The challenge is there is only one opportunity to get it right. An important role for healthcare professionals in supporting dying is to help anticipate what may be needed for a particular patient and family. An important question to ask is, given the potential complexity of a home death, are there adequate human resources available to care for the person

and their family safely in their current place of care (this may include home/retirement home/ long-term care residence/hospital/ hospice)? If they are vulnerably housed, what new challenges might this pose? (See Chapter 30.)

Our current healthcare system is under mounting pressures with an exponentially rising ageing demographic with multi-morbidities. Unfortunately, this has the potential to increase the risk of patients either being discharged home quickly from hospital before appropriate plans can be developed and put in place for end-of-life care, or being unable to access an appropriate hospital or hospice bed for the care they need due to bed resource issues. Both of these situations have the potential to increase emergency room visits that add extra stress to patients, families, and healthcare professionals, as some of these people will die on a stretcher in the emergency department. Alternatively, they remain at home without adequate supports in place, leading to poor symptom control and increased patient and family distress.

In planning for end-of-life care, we need to look at the patient's estimated prognosis and needs for care. Is it down days to hours or are there still days to weeks left to prepare? Time is a very important consideration in the planning for human resource and equipment needs. What supports are available, and how quickly these can be arranged, may differ in different communities.

When considering needs, will someone be available who can be responsible for medication administration? Will they be able to help with the patient's physical needs? Are there others in the circle to support? If the answer is no to these supports, does the local healthcare system or care facility have the resources to fill these roles? We also need to anticipate practical needs such as walkers, commodes, electric beds, and other assistive devices. Are they available in a particular community? Are they accessible in a timely fashion? Are they covered or cost-prohibitive?

In developing an end-of-life care plan, it is very important to clearly articulate who will provide personal care, symptom monitoring and assessment, and treatment when needed. Primary palliative care supports must be available 24 hours a day, 7 days a week, with access to specialist palliative care advice when needed.

Question 3. Are you prepared to care for this dying patient?

Healthcare professionals need to know what normal dying looks like and how to provide symptom management during the dying process, so that we can provide good information and best supportive care to patients and their families. It is important to remember that this may be the first time a family may be going through the death of a loved one and it can be frightening when they do not know what to expect.

Self-awareness is an essential tool for healthcare professionals in being able to provide good care to the dying. Self-awareness involves a combination of awareness of patient and family needs, the work environment, and personal knowledge and awareness of how all of these impact your ability to perform and thrive in your role. Both personal and professional experiences of being with people with life-limiting conditions and who have died can have significant influence on how you respond.[3] Negative experiences can lead to avoidance, inappropriate treatment, providing false hope, and burnout. Positive experiences can lead to being more empathetic, more engaging with patients and families, and being able to discuss more appropriate treatment options.[4]

As healthcare professionals, we can become more self-aware by accepting our own feelings, imagining what the patient's and family's feelings are, watching for patterns of responses, and trying to understand them. We also need to be able to separate our personal feelings from the current patient encounter, thereby being present and focused on their needs.

Caregivers are usually able to manage if given enough information, guidance, and support. It can be challenging if there is only one caregiver. Extra attention needs to be given to the caregiver

and watch for caregiver fatigue. Lack of sleep on the part of the caregiver can lead to increased frustration and errors.

Case 19.1 (continued)

H.H. wants to remain at home to die. H.H.'s family is supportive and will do what is necessary to help support her at home. Now what do you do?

Question 4. What do H.H. and her family need now in order to plan for a home death?

Now that the patient has expressed her wish to remain at home for her death, it is important, with her permission, to open the discussion up with her family. It would be extremely difficult for her to have a home death without her family participating, unless she has the resources to hire all private care.

Above all else, H.H. and her family need information and guidance. Most people of their daughter's generation are likely to have never gone through a home death. Regardless of location, it is important to help the family understand what is normal to expect during the dying process and what physical symptoms and changes to anticipate. If dying at home, the patient and family need to understand how the home care team will help provide care in the home. Having regular check-ins and knowing who to call 24/7 for any concerns and problems that arise will help ensure they feel well supported. A written plan for end-of-life care can provide an additional layer of support for families, ensuring clear communication with the healthcare team.

There are several important considerations in developing an end-of-life care plan. These include an approach to deprescribing, managing common symptoms at end of life, and alternative routes for medication administration when the oral route is no longer possible.

1. *Deprescribing.* Any medication that is not adding to the person's quality of life and providing comfort can be discontinued or weaned in the last days and hours of life. Medications that primarily have long-term preventative roles, rather than immediate improvement to well-being and control of symptoms, can become an extra burden with little benefit at the end of life. For example, a statin for cardiac disease or bisphosphonate, calcium, or vitamin D for osteoporosis would not be providing comfort and should be discontinued if consistent with patient wishes and goals. Other medications may be helpful for symptom relief and quality of life, and can be continued for as long as the patient does not find them burdensome to take and maintains a safe oral route for administration. An example of this would be beta blockers for arrhythmias or a proton pump inhibitor for gastro-oesophageal reflux disease. As a general approach, all medications that a person is on should be evaluated for burden/benefit and be discontinued when more of a burden. Most oral medications can be discontinued when you lose the oral route during the last days to hours of life, except those with a primary intent of providing comfort for which you may need an alternative route of administration (i.e. oral morphine changed to subcutaneous morphine).
2. *Physical symptoms/changes that may arise in the last days and hours of life*. There are several normal symptoms and physical changes that can occur prior to death. Proactively discussing these with caregivers, as well as providing plans to address them, allows caregivers and families to be less frightened and more comfortable with the process. Having this information in writing is very helpful for families to review or to discuss with other family members who were

not present during previous discussions. An example can be found at https://sunnybrook.ca/content/?page=what-to-expect-dying-last-hours-life.[5] The most common symptoms/changes include:

- *Breathing*: breathing patterns change at end of life. Breathing can appear shallow, slow, and rapid, or be 'noisy' from secretions. Explaining to families what to expect with these neurological changes can alleviate fears that a loved one is 'short of breath' or 'drowning'. Common breathing patterns that occur in the actively dying phase include: apnoeas and Cheyne–Stokes respirations which are characterized by recurrent central periods of not breathing, alternating with a crescendo–decrescendo pattern of tidal volume. It is important to reassure the family that these changes are not uncomfortable and their loved one will not have any awareness of these changes.
- *Respiratory secretions*: excessive respiratory secretions (previously referred to as the 'death rattle') are very common at the end of life and can result from the loss of swallowing reflex, excessive production of sputum (i.e. if a patient was hydrated with intravenous fluids just prior to death), and ineffective cough reflex. Other causes of excessive secretions include respiratory infections and pulmonary oedema. Most often, the patient will have no awareness of this; however, it can be very distressing to the family who may feel that their loved one is 'drowning' or having difficulty breathing. It is important to provide clear education about this and provide information about approaches to management. Non-pharmacologic manoeuvres are usually sufficient, including simple repositioning of the head. Suctioning should be avoided, as it can be distressing to the patient and family. There is limited evidence for the use of anticholinergic medications; however, commonly, 1% atropine ophthalmic drops (two drops sublingually every 4 hours as needed), hyoscine hydrobromide (scopolamine 0.2–0.4 mg every 4 hours as needed), and glycopyrrolate (0.2–0.4 mg every 2 hours as needed) can be trialled if distressing symptoms or more copious thin secretions are an issue. Glycopyrrolate does not cross the blood–brain barrier and is therefore less sedating than the others and preferred for elderly patients; however, there is no clear advantage of one versus another.[6] If the person has pulmonary oedema, then furosemide 20 mg subcutaneously can be trialled.
- *Delirium*: delirium in the last days and hours is very common and is sometimes referred to as 'terminal restlessness' or 'terminal delirium'. The preferred terminology is 'delirium at end of life' or an 'irreversible delirium'. Delirium at end of life occurs in up to 88% of people and it should be carefully screened for and treated. Unfortunately, delirium is often misinterpreted as increased pain and can be very upsetting to the family and caregivers. Clearly explaining that this restlessness/agitation is due to delirium, and not pain, can alleviate concerns that a loved one is developing increased pain that is not controlled by their analgesic medications (see Chapter 12 for management of delirium). Earlier in the trajectory of a person's condition, delirium should be screened for and potentially reversible causes identified and treated. Unfortunately, in the last days and hours of life, delirium is often multifactorial and irreversible. It is imperative that symptoms of agitation and restlessness secondary to hyperactive delirium be aggressively managed, and palliative sedation should be used, when appropriate, for refractory symptoms, as described in Chapter 20. Severe agitated delirium at end of life is the most common indication for palliative sedation therapy.[7]
- *Loss of oral intake*: it is normal for patients to stop eating and drinking at the end of life, and explaining this natural dying process to families, including why artificial hydration and nutrition would not be beneficial in the last hours to days of life, can alleviate fears that a loved one is 'starving' to death.[8] If hydration is already being used for specific symptom management, healthcare professionals should discuss the potential of discontinuing it

with the family prior to stopping, in order to ensure their understanding of the rationale, including the potential harms with hydration at end of life. Some families are too distraught at the thought of completely discontinuing hydration, so you may need to continue at a reduced amount, with an understanding that ongoing monitoring and regular reassessment will be carried out to ensure no adverse consequences. If intravenous access is difficult to obtain or is not consistent with goals of care, intravenous fluid can be run subcutaneously (hypodermoclysis) at a rate of up to 60 ml/h if the site will tolerate. If worsening symptoms occur because of hydration, then fluids should be discontinued.

- *Incontinence*: becoming incontinent at the end of life can cause a huge loss of dignity for many people. This is why it is so important for all caregivers to respect this change and try to pay additional attention to dignity-conserving care.[9]
- *Mottling*: skin mottling occurs in the dying process due to changes in perfusion. It is seen as a change in colour and decreased temperature of the skin in both the upper and lower extremities, especially the hands and feet, and can wax and wane prior to death. It is important to help families and caregivers understand this normal phenomenon and reassure them that it is not uncomfortable.

3. *Alternate routes for medication administration*: it is inevitable that dying patients will lose their oral route for medication administration as they approach death, and certain symptoms will require continued treatment using an alternative medication route, regardless of their place of care. This is usually done via the subcutaneous route. Administration of medications for dyspnoea and/or pain, delirium or restlessness/agitation, anti-nauseants, and, on occasion, medications for palliative sedation for intractable symptoms can all be given subcutaneously. Instructions on providing this alternate route for medications and ensuring access are critical to success of a home death[13]. Some palliative care programmes have pre-prepared symptom response kits with essential subcutaneously administered medications that may be required, and they are placed in the home before they are needed. In other areas, the medications are ordered and placed in the home close to when needed. Orders for home care nursing outline how and when to stop oral medications, insert subcutaneous lines, preload medications, and instruct the family on how to administer. Medication calendars are prepared to clearly show what medication is to be given when and for what purpose. This is reviewed with each family member that will take on administration responsibilities. It is important to tailor the medication plan to the individual and not start medications just because someone is dying. The medications and the rationale for their use need to be clearly communicated with the patient and their family/caregivers and documented in the chart.

Case 19.1 (continued)

H.H. now has decreased level of consciousness and is unable to swallow in her last days to hours of life.

Question 5. What would medication planning for H.H. look like?

An example of medication planning is as follows. H.H. was on:

Morphine slow-release (SR) 30 mg po q12h—for pain and dyspnoea.

Morphine 5 mg po q1h PRN—for breakthrough pain or dyspnoea.

Metformin 500 mg po twice a day—for non-insulin-dependent diabetes.

Hydrochlorothiazide 25 mg po every morning (qam)—for hypertension.

Dexamethasone 1 mg po qam—for chest wall pain and dyspnoea.

Senna 17.6 mg (two tablets) po every night at bedtime—for constipation.

We want to replace essential medications to the subcutaneous route for ongoing symptom management. The orders would most likely include:

1. When no longer able to swallow, insert subcutaneous lines, preload medication, and instruct family on how to administer.
2. Prepare medication calendar for the family to follow.
3. Morphine 5 mg subcut q4h and 2.5 mg subcut q2h PRN for pain or dyspnoea [morphine SR 30 mg po q12h = 60 mg po/day = 30 mg subcut/day—divide by 6 = 5 mg subcut q4h; breakthrough dose = 10% of daily amount (30 mg subcut/day) or half the dose of the short-acting equivalent, so will use 2.5 mg subcut q1h PRN].
4. Dexamethasone 1 mg subcut qam (continue in case helping pain and dyspnoea).
5. Stop metformin, hydrochlorothiazide, and senna.
6. Bisacodyl suppository daily PRN or every 3 days if no bowel movement (you could also use glycerine suppository or an enema if the patient prefers).

Question 6. What psychosocial issues may arise at the end of life?

The end of life is often an emotional time for families and caregivers. If appropriate, have a clear support tree identified and open a discussion to assess if anyone in the tree may need some additional support or guidance (i.e. bereavement support or how to speak to children about death and dying). Families and support networks are often scattered across the country and around the world. While many are aware of various communication options such as Skype and FaceTime, some may be grateful for help reaching out to distant loved ones. Pets are also often important members of families, and helping patients explore options for pet visitation or care can be very reassuring to patients and families.

Grief, both anticipatory and following the death, are normal experiences for families and caregivers. Stephen Jenkinson said, 'Grief is the love you feel for what you have lost; love is the grief for what you haven't lost yet'.[10] Helping people to understand the normalcy of grief and its relationship to the love for the person is important. Many people will either try to suppress their own grief or try to help someone 'get over' their grief. Knowing about support systems, including other family members, friends, spiritual community, or others, from which they can get support and encouraging them to connect with them may be helpful. Directing them to online supports such as MyGrief.ca[11] may also be helpful (see Chapter 34). Referring to a psychologist or psychosocial spiritual counsellor on the team may also be of tremendous benefit. Obtaining a spiritual history is generally greatly appreciated by patients and families. Asking about cultural, religious, or other spiritual support systems and rituals that are important to the person is important in providing dignity-conserving care.

Question 7. What if H.H. has an implanted cardioverter–defibrillator (ICD)?

ICDs have become more common in many parts of the world, so it is important to ask specifically about this in making end-of-life care plans, especially if someone says they have a 'pacemaker'.

Some patients use the term 'pacemaker' when they actually have an ICD. You can die comfortably with a pacemaker in place without needing to do anything to it. An ICD, on the other hand, may start giving shocks as someone is actively dying, which is very distressing to the patient (it feels like getting kicked in the chest), the family, and the caregivers. Identifying this early on allows for discussions about turning off the defibrillator which does not cause any discomfort [14] (see Chapter 23 for additional information and discussion on ICDs).

Question 8. How can we help prepare the family for the time of death?

It is common for there to be a quiet time before death when the patient is no longer communicating. This time can be challenging for families as it is often the first time they are left with only their feelings and they are often also quite fatigued. It is not uncommon for them to worry about their loved one suffering, even when the patient is comfortable with no signs of distress. This is often a sign of their own grief, emotional distress, and fatigue. It is important for healthcare professionals to be comfortable with this time and provide reassurances. We want to be sure we are diligently assessing for signs of distress and providing support to the family when all is going well.

Question 9. What needs to happen at the time of death?

As local rules and procedures can vary across jurisdictions, it is important to know your local processes for death notification and transfer of the body to a funeral home or crematorium. Your local medical examiner/coroner or palliative care specialty team should be able to provide advice if you are not sure.

It is important to ask the family in advance about funeral home or other arrangements, as well as whether there are any plans for organ or scientific tissue donation. This allows the family to emotionally and physically prepare for death, including making arrangements for any particular religious or cultural rituals or rites that need to happen. The funeral home can be advised of an expected death at home. In most places, arrangements can be made to avoid the need for an emergency response call and deployment of an ambulance at the time of death, but this needs to be confirmed in the local area.

Question 10. When does the medical examiner/coroner need to be called?

Be sure to check with your local jurisdiction, but in general, physicians and nurse practitioners should notify the medical examiner in certain circumstances,[12] including:

1. When the cause of death is unknown or cannot be determined.
2. When the death is known or suspected to be the result of violence, accident, poisoning, or suicide.
3. When the death is unexpected.
4. When the decedent was not previously under the care of a physician.
5. When improper or negligent treatment of the decedent is suspected.
6. When the death has occurred soon after a fracture or other injury, no matter how trivial.
7. When there is reason to believe that the death occurred as a result of suspected misadventure, negligence, or accident on the part of a physician or other healthcare provider.

8. When a still birth or a neonatal death has occurred where maternal injury has occurred or is suspected either before admission or during delivery.
9. When the death occurs within 10 days of an operative procedure or under initial induction, anaesthesia, or recovery from anaesthesia.

Case 19.1 (continued)

Due to a lack of family and community resources to provide 24-hour care at home, H.H. opts to go to her local community hospital for her last days of life. Arrangements are made for a direct admission, and with clear communication, her transition from home to hospital goes well. Her goals of care are shared with her attending staff and she and her family are provided with compassionate, competent care during her last days and hours.

Question 11. What do you say when someone dies?

It is very important at the time of death or after to pay close attention to our communication. Platitudes like 'they're in a better place now' or 'it was God's will' tend not to be helpful and can be hurtful to some. Expressing your condolences and asking if anyone has any questions is often enough. Bereavement resources can be offered to the family. For further information on bereavement, see Chapter 14.

Pearls

- Know what to expect in the last days and hours of life.
- Help educate patients and families about the natural changes at end of life.
- Reassure patients and families on how distressing changes can be managed.
- Encourage ACP and use it to develop goals of care and care plans. Do your own!
- Be aware of your own feelings and ensure you care for yourself and also encourage team health and well-being.

References

1. **Wolfelt AD** (2016) *Why is the funeral ritual important?* Center for Loss and Life Transition.
2. **KidsGrief.ca**. *Talking with kids and teens about serious illness, dying and death*. https://kidsgrief.ca
3. **Sanchez-Reilly S** (2013) Caring for oneself to care for others: physicians and their self-care. *J Support Oncol*, **11**(2), 75–81.
4. **Showalter SE** (2010) Compassion fatigue: what is it? Why does it matter? Recognizing the symptoms, acknowledging the impact, developing the tools to prevent compassion fatigue, and strengthen the professional already suffering from the effects. *Am J Hosp Palliat Care*, **27**(4), 239–42.
5. **Sunnybrook Health Sciences Centre**. *What to expect in the last hours of life*. https://sunnybrook.ca/content/?page=what-to-expect-dying-last-hours-life
6. **Kintzel P**, **Chase S**, **Thomas W** *et al*. (2009). Anticholinergic medications for managing noisy respirations in adult hospice patients. *Am J Health Syst Pharm*, **66**, 458–64.
7. **Bush SH**, **Lawlor PG**, **Ryan K**, *et al*. (2018) Delirium in adult cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol*, **29**(Suppl 4), iv143–65.
8. **Hui D**, **Dev R**, **Bruera E** (2015) The last days of life: symptom burden and impact on nutrition and hydration in cancer patients. *Curr Opin Support Palliat Care*, **9**(4), 346–54.

9. **Chochinov H** (2002) Dignity-conserving care—a new model for palliative care. Helping the patient feel valued. *JAMA*, **287**(17), 2253–60.
10. **Jenkinson S** (2015) *Die Wise: A Manifesto for Sanity and Soul*. https://orphanwisdom.com/die-wise/
11. **Canadian Virtual Hospice**. *MyGrief.ca—Because losing someone is hard . . .* http://www.mygrief.ca/
12. **College of Physicians and Surgeons of Nova Scotia** (2013) *Professional standard on physician obligations regarding certification of death*. https://cpsns.ns.ca/wp-content/uploads/2017/10/Physician-Obligations-Regarding-Certification-of-Death.pdf
13. **Jansen K**, **Haugen DF**, **Pont L**, **Ruths S** (2018) Safety and effectiveness of palliative drug treatment in the last days of life—a systematic review. *J Pain Symptom Manage*, **55**(2), 508–21.e3.
14. **CorHealth Ontario**. *When to consider implantable cardioverter defibrillator (ICD) deactivation*. https://www.heartandstroke.ca/-/media/pdf-files/canada/health-information-catalogue/en-when-to-consider-icd-deactivation.ashx

Chapter 20

Continuous palliative sedation therapy

Leonie M. Herx

Attitude

To enable the learner to:

- Understand that continuous palliative sedation therapy (CPST) is a specialized medical intervention for a select group of patients with refractory symptoms at the very end of life.
- Differentiate between CPST and euthanasia.
- Consider the ethical issues surrounding CPST.
- Understand that clinical guidelines are essential in the practice of CPST.

Skills

To enable the learner to:

- Obtain consent from the patient and/or substitute decision-maker (SDM) for provision of CPST.
- Demonstrate proportionate titration of medications for CPST.
- Maintain CPST and use ongoing monitoring for medication effects and side-effects.
- Demonstrate self-awareness and reflective practice when providing CPST.

Knowledge

To enable the learner to:

- Define CPST.
- Describe the criteria that need to be fulfilled in order to initiate CPST.
- List the indications for CPST.
- Describe pharmacological options for the provision of CPST.

Case 20.1

B.B., 53, is admitted to the palliative care unit (PCU) for end-of-life care. His PPS is 20%. He has lung cancer with brain metastases. His goals of care are focused on comfort measures, and his power of attorney and advance directives identify his wife as his SDM. His family could not cope with his restlessness and agitation at home. On the PCU, no reversible causes for his delirium were identified. He was started on around-the-clock and as-needed neuroleptic medications for management of his delirium. Despite titration of these medications, his symptoms remain poorly controlled and his agitation is worsening. His wife asks you to do something else to relieve his apparent distress and make him comfortable.

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Question 1. What options are there for sedation at the end of life?

Various types of sedation are used near the end of life, including temporary sedation to treat a reversible delirium (see Chapter 12 on delirium) and the use of sedating medications to manage symptoms of an irreversible, agitated delirium at end of life (see Chapter 19 on the last days and hours). Rapid onset of sedation, usually accomplished through boluses of midazolam, may also be required acutely for catastrophic terminal events such as massive haemorrhages. These are different from CPST, which is a specialized medical intervention for refractory symptoms in the last days of life that have not responded to other treatments. In CPST, a symptom is understood to be irreversible and medications are carefully titrated to control the symptom at the lightest sedation level and the lowest medication dose possible, and continued until the patient's death.[1] Hence the term 'continuous palliative sedation therapy' is preferred over the more general term 'palliative sedation' to differentiate this practice from the other types of sedation used for palliative treatment at the end of life.[2]

In B.B.'s case, the delirium was found to have no reversible causes and symptom management was unsuccessful despite adequate titration of standard neuroleptic medications. In such cases when intractable symptoms are refractory to usual medical management during the last days of life, CPST can be used.

Question 2. What is continuous palliative sedation therapy?

CPST is defined as the process of inducing and maintaining sedation, in the last hours and days of life, for the relief of suffering caused by intractable symptoms when all appropriate alternative interventions have failed to provide adequate symptom relief. Death is expected imminently within hours to days (less than 2 weeks) from progression of the underlying illness (this includes death that is expected from withdrawal of life-sustaining therapies, such as ventilatory support, when they are no longer beneficial to the patient). The intention of CPST is relief of suffering, and not to shorten life or to bring about complete loss of consciousness through sedation, although the latter is sometimes necessary to relieve the suffering.[2] Sedation is induced and maintained proportionately to the level necessary to relieve the refractory symptoms and requires careful monitoring and adjustment of medication dosing to ensure the lowest effective dose is used.[1]

Question 3. Why is CPST only indicated during the last hours and days of life?

Life expectancy is important in the context of providing CPST because deeply sedated patients are unable to drink, and we know that some individuals will require deep sedation in order to relieve their symptoms. Death from the natural progression of the underlying condition should be expected to occur in equal to, or less time than, dehydration from CPST, so that death occurs from the underlying condition, and not dehydration.[3]

International guidelines and frameworks for CPST are consistent in their requirement that death must be imminent, with a life expectancy of hours to days or up to 1–2 weeks.[1,2,4]

Question 4. What are refractory symptoms?

Symptoms are deemed refractory when all reasonable and available treatment options to manage a patient's symptoms and relieve their suffering have been explored and provided.[2] Refractory

symptoms should be differentiated from difficult-to-manage symptoms, and therefore, consultation with a palliative care specialist is recommended to ensure that there are no other methods available for palliation of symptoms that are tolerable to the individual within the limited time frame. The most common indications for palliative sedation are refractory symptoms from agitated delirium, severe dyspnoea, and pain.[1,5]

CPST for refractory existential suffering alone is controversial. Existential suffering is defined as a fear of dying or of death itself, often associated with loss of meaning of life or purpose, loss of dignity, hopelessness, demoralization, and perceiving oneself to be a burden to others.[6] Existential suffering can be associated with intensification of physical symptoms or can exist by itself. The Canadian CPST Framework recommends that CPST for purely existential symptoms only be considered in rare cases when skilled multidimensional management directed at existential, psychological, and physical dimensions have been attempted, in consultation with relevant experts in these areas, and that all other criteria for CPST [1,2,7] must be met, as outlined in Box 20.1 below. However, there is a lack of consensus internationally regarding the definitions and assessment of existential suffering, the intensity and refractoriness of existential suffering, given its subjective nature, and the application of ethical principles used to support positions regarding the use of CPST for existential suffering.[8] As a result, there continues to be differences of opinion regarding existential suffering as a primary indication for CPST and further research is needed in this regard. Given these complexities, it is recommended that all patients being considered for CPST due to existential suffering have a specialist palliative care team consultation. The criterion that death is expected within the final hours to days remains for all guidelines.

Box 20.1 Recommended criteria for initiation of CPST

1. Symptoms are refractory to all other treatments that are possible and available within the limited time frame and that the patient can tolerate (it is strongly recommended that the patient be assessed by a palliative care consultant to ensure all potential treatment options have been provided).
2. Death is imminently expected within hours to days (less than 2 weeks).
3. The patient or his/her SDM understands the outcome of the underlying illness and what to expect during the dying process.
4. The patient or his/her SDM understands the goal of CPST is to alleviate refractory suffering, and not to hasten death, and provides consent to CPST.
5. The goals of care of the patient are comfort-focused care. No life-prolonging or lifesaving therapies would be initiated or continued unless directly providing symptom management and comfort.

Sources: data from Cherny NI, Radbruch L. 'European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care'. Palliat Med 2009; 23: 581–593.1; Dean MM, et al. 'Framework for Continuous Palliative Sedation Therapy (CPST) in Canada'. J Palliat Med 2012; 15: 1–6.2; and De Graeff D, Dean M. 'Palliative sedation in the last weeks of life: a literature review and recommendations for standards'. J. Palliat Med 2007; 10 (1): 67–85.8

Question 5. How is continuous palliative sedation therapy provided?

CPST is typically provided through use of short-acting benzodiazepines, most commonly a midazolam infusion or sedating neuroleptics such as methotrimeprazine. For severe cases, patients may require barbiturates or propofol. Medications are titrated for effect to the lowest dose possible to achieve comfort. Level of consciousness should be lowered only as far as is necessary to relieve suffering, and is thereby 'proportionate' sedation. Ongoing monitoring should be provided for the patient's comfort, level of sedation needed to achieve comfort, and potential adverse effects. Patients should be regularly checked for urinary retention, pressure sores, and other sources of discomfort. Ongoing mouth and bowel care should be provided. Patients already on opioids for symptom management should have their opioids continued at current doses, but not escalated. Opioids should NOT be used specifically for CPST because to achieve sedation will require toxic doses, leading to opioid-induced neurotoxicity and respiratory depression, which will cause discomfort and may hasten death.[2]

Prior to initiating CPST, the patient and/or their SDM must be counselled, so they understand the goal of CPST, how it will be administered and monitored, and what to expect during the dying process. The patient or their SDM must provide consent for CPST. Ongoing comfort-focused personal care must be maintained for the patient, and supportive care provided for the family. All patients receiving CPST require a 'do-not-resuscitate' or 'comfort-focused' care designation. The medical care team needs to be aware of the goals of care and the proposed plan for CPST.

Question 6. What are the first-line medications for providing CPST, and the advantages and disadvantages of each?

Short-acting benzodiazepine infusions, typically midazolam, are used first line for ease of rapid titration due to a very short onset of action (1 minute) and time to peak effect (less than 5 minutes with a bolus). Rare patients can have a paradoxical excitatory reaction. Infusions can be given subcutaneously (SC) or intravenously (IV), depending on IV access and the setting of care. An initial loading dose of 2.5–5 mg of midazolam should be given and then an infusion started at 1–5 mg/hour. The infusion should be titrated by 1 mg every 15 minutes until the desired level of sedation is achieved. Patients have to be carefully monitored for comfort and dosage of the infusion adjusted as needed to maintain the level of sedation needed to achieve this. A sedation scale is often used to monitor and communicate between healthcare providers as to the level of sedation needed for comfort. The Richmond Agitation Sedation Scale (RASS) is one such example, used most often in the intensive care setting and modified for use in palliative care.[9] The recommended therapeutic range for continuous midazolam infusion is 1–10 mg/hour. If unable to maintain comfort, ensure consultation with an expert who can provide support for higher dosing levels or recommendations on second-line agents.

Injectable sedating neuroleptic medications such as methotrimeprazine can be used as an alternative to continuous midazolam. This may be necessary in a setting where an infusion is not possible and intermittent SC medications are required. Methotrimeprazine has a very long half-life and a slower onset of action, so it takes substantially longer to achieve steady state of increased doses. Patients must be monitored for extra-pyramidal side-effects. Rarely, it can cause seizures due to lowered seizure threshold. The starting dose would be to give 12.5–25 mg SC every 4 hours and every 1 hour as needed. This can be titrated to 25–37.5 mg SC every 4 hours.

Question 7. What are the second-line medications that can be used for CPST?

If not already involved, consultation with a palliative specialist is strongly advised when symptoms are not well controlled on high doses of midazolam or methotrimeprazine. Second-line therapies include phenobarbital and propofol, depending on the setting. Phenobarbital is given as a bolus of 1–3 mg/kg, followed by an infusion of 0.5 mg/kg/hour, which can be given either SC or IV. The typical therapeutic range is 50–100 mg/hour. The disadvantages of phenobarbital include a slower time to peak effect of 30 minutes and it has a long half-life of 50–120 hours, which can make it difficult to titrate. Adverse effects to monitor for include paradoxical excitation and, rarely, Stevens–Johnson syndrome. Propofol can also be used effectively for palliative sedation but is only given IV and is restricted to an acute care inpatient setting with staff trained in its administration and use. Propofol is typically given in an intensive care setting or an acute PCU. An initial IV loading dose of 0.5–1 mg/kg/minute is given over 5 minutes, followed by a continuous IV infusion of 1–4 mg/kg/hour, titrated 0.5 mg/kg/hour every 5–10 minutes as needed until sedation is achieved. Propofol is advantageous because it has a fast time to peak effect of 5 minutes and can be titrated very quickly to an effective dose. However, it must be run as an infusion due to a short duration of action of less than 10 minutes. Rhabdomyolysis, cardiac arrhythmias, and renal failure are rare side-effects.

Question 8. Does B.B. meet the criteria for CPST and what next steps would you follow?

B.B. is imminently dying in the last days of his life and has an irreversible delirium, and his severe agitation has not responded to titration of neuroleptic medications at maximal doses (reviewed with the palliative care consulting physician). He would meet the criteria for CPST. His wife understands he is dying in the coming hours or short days and wants his care focused exclusively on comfort. You discuss the option of CPST and she is relieved there is something that might be able to alleviate his suffering. For the next steps, you ensure she understands how CPST will be provided and monitored and what to expect during the dying process. She wants to know if providing CPST will hasten his death.

Question 9. Does CPST hasten death? How is CPST different from euthanasia?

Palliative sedation does not hasten death when provided in accordance with recommended guidelines and frameworks.[10,11,12,13,14,15,16,17,18] In a systematic review of over 600 patients receiving palliative sedation, no substantial differences in survival were found between sedated and non-sedated patients.[10] A further prospective study showed that CPST had no effect on overall survival.[11] Misunderstandings and concerns raised regarding CPST causing hastened death are mostly in relation to sedation being used inappropriately, such as before death is imminent, and when given well beyond the proportional doses needed to palliate suffering.[2]

CPST is distinct from euthanasia in both the intention and approach. In euthanasia, the intention is to cause death by the administration of a lethal dose of drugs. In CPST, the intention is to relieve refractory symptoms through the proportionate titration of medication to the lowest level necessary to achieve comfort. Death is not a criterion for the success of treatment in CPST, as it is in euthanasia.[19] There is no intention to shorten life or to bring about complete loss of consciousness in CPST, although the latter may sometimes be necessary to alleviate symptoms.

CPST correctly practised is distinct from euthanasia and is considered an appropriate palliative intervention.[1,2]

Case 20.1 (continued)

You explain the difference between CPST and euthanasia to B.B.'s wife and the care team to ensure everyone understands the goals for CPST and how it will be provided, including close monitoring for therapeutic effects and side-effects. B.B.'s wife is relieved that her husband's life will not be shortened and that he will die from natural progression of his underlying cancer. B.B.'s wife provides consent to initiate CPST for her husband and you order a SC midazolam infusion, as per your local institutional CPST policy. The midazolam infusion is titrated proportionately to relieve his agitation and it is determined that his agitation is well controlled at a moderate sedation level of RASS −3. The team continues to provide regular personal care to B.B. and support to his wife. B.B. dies 2 days later and his wife feels he was very comfortable.

Question 10. What are some of the ethical considerations with CPST?

Palliative care clinicians and ethicists consider CPST to be an important and ethically acceptable therapy in the care of select patients at the very end of life with otherwise refractory distress.[1,2,20] It should be a last resort when all other options have been exhausted or are not possible due to the resources available or the limited time frame. The use of CPST must be applied carefully in order to minimize potential risks, harms, and problematic practices that may arise from the injudicious or unskilled use of sedation. Misuse of CPST occurs when clinicians sedate patients with the primary goal of hastening death, through the deliberate use of deep sedation in patients who are not clinically appropriate (e.g. who do not have refractory symptoms or are not imminently dying) or through the deliberate use of doses of medications that far exceed what is necessary to provide comfort.[1,20]

Sedation at the end of life must be judiciously applied only when there is consensus 'that the harm of suffering warrants the harm of reduced consciousness, and sedation should only be deep enough to palliate'.[2] It should be determined that symptom relief could not be obtained without the intentional lowering of consciousness, and consciousness should be lowered only as far as necessary to relieve suffering.[2] Thereby, sedation is a reasonable, proportionate response to relieve refractory symptoms that cannot be controlled in any other way.

Patients who are sedated have a potential risk for respiratory depression, aspiration, and haemodynamic compromise, and thus it is argued that under some circumstances, death may be unintentionally hastened in CPST.[21] The ethical principle of double effect has been used historically to justify this potential risk of CPST, wherein there lies a moral distinction between the initial intention and foreseen, but unintended, consequences of CPST (i.e. that the medications used in CPST *may* potentially shorten life but are not intended to do so). Therefore, this possible unintended consequence is acceptable.[22] However, when CPST is provided with rigorous application of recommended guidelines and frameworks for a carefully select group of patients (as outlined in Box 20.1), it has not been shown to shorten life.[10,11,12,13,14,15,16,17,18]

There are ongoing misconceptions that CPST is a form of euthanasia. However, CPST and euthanasia are categorically distinct, with very different intentions and methods for provision, as described above (see Question 8). It is important that these differences be clearly understood by patients, families, and the healthcare professionals involved in providing care.

Question 11. Why are clinical practice guidelines and frameworks important for CPST?

Given the potential for misuse or abuse of CPST, as well as the ongoing confusion between CPST and euthanasia, it is essential that clinical practice guidelines and frameworks are in place and used to set and maintain rigorous standards for practice. This is important in order to ensure patient safety, as well as the credibility and reputation of the discipline of Palliative Medicine, responsible healthcare professionals, and institutions.[1,2,20,23]

The Canadian Society of Palliative Care Physicians recommends that all physicians practising CPST create or adopt a specific policy on CPST for their practice group or institution.[24] There are numerous frameworks and guidelines that can be used as a resource, as summarized in Box 20.2. These frameworks delineate the indications, decision-making, medications, and monitoring requirements for delivering safe and effective CPST.

Question 12. What is the importance of reflective practice in providing CPST?

Provision of CPST is complex by nature due to the implication of intractable symptoms, and clinicians will often have emotional responses when faced with the refractory suffering of a patient. It is critical that clinicians understand their own hopes, values, and emotions when responding to patient and family distress, and are aware of how this affects their interpretation of that person's suffering. It is easy to impose one's own values on any situation. Decisions around care should be determined based on evidence-based practices and the goals of the patient, rather than what a clinician would want for themselves in a similar situation. Thus, self-awareness and reflective practice are the cornerstones of professional practice for providers of palliative care, especially

Box 20.2 Useful practice guidelines and frameworks on CPST

Regional Canadian guidelines

1. Alberta Health Services (2018) *Provincial Clinical Knowledge Topic: Palliative Sedation, Adult—All Locations V 1.0*. https://extranet.ahsnet.ca/teams/policydocuments/1/klink/et-klink-ckv-palliative-sedation-adult-all-locations.pdf
2. BC Centre for Palliative Care (2017) *Refractory Symptoms and Palliative Sedation*. https://www.bc-cpc.ca/cpc/wp-content/uploads/2019/06/17-RefractorySymptomsAndPalliativeSedationGreyscalePrint.pdf
3. Collège des Médicins du Québec (2016) *Palliative Sedation at the End of Life*. http://www.cmq.org/publications-pdf/p-1-2016-08-29-en-sedation-palliative-fin-de-vie.pdf
4. Canadian Society of Palliative Care Physicians (2017) *Statement on Continuous Palliative Sedation Therapy*. https://www.cspcp.ca/wp-content/uploads/2017/11/CSPCP-Statement-CPST-FINAL.pdf
5. Winnipeg Regional Health Authority (2017) *Sedation for Palliative Purposes Guideline*. http://www.wrha.mb.ca/extranet/eipt/files/EIPT-045.pdf

Box 20.2 *(continued)*

International guidelines

1. Canada: Dean MM, Cellarius V, Henry B, Oneschuk D, Librach SL (2012) Framework for continuous palliative sedation therapy (CPST) in Canada. *J Palliat Med*, **15**, 1–6.
2. Europe: Cherny NI, Radbruch L (2009) European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. *Palliat Med*, **23**, 581–93.
3. Japan: Morita T, Bito S, Kurihara Y, Uchitomi Y (2005) Development of a clinical guideline for palliative sedation therapy using the Delphi method. *J Palliat Med*, **8**, 716–29.
4. Netherlands: Royal Dutch Medical Association (KNMG) (2009) *Guidelines on Palliative Sedation*. https://www.knmg.nl/web/file?uuid=f63bc1b5-ba8d-405b-b901-d3ccc37b6123&owner=5c945405-d6ca-4deb-aa16-7af2088aa173&contentid=550 (available in English).
5. New Zealand and Australia: The Australian and New Zealand Society of Palliative Medicine (ANZSPM) (2017) *Palliative Sedation Therapy Guidance Document*. http://www.anzspm.org.au/c/anzspm?a=sendfile&ft=p&fid=1500595939&sid=
6. United States: National Hospice and Palliative Care Organization (NHPCO) (2009) Position Statement and Commentary on PS. https://www.nhpco.org/wp-content/uploads/2019/04/NHPCO_Pall-Sedation-Ther_JPSM_May2010.pdf

in the context of CPST. In addition, because of its confusion with euthanasia, CPST can be morally and ethically challenging for some healthcare professionals. Clinicians must understand their own ethical and moral viewpoints on this and understand the differences between euthanasia and CPST, so this can be clearly explained and understood by patients, families, and the larger healthcare team.

References

1. **Cherny NI**, **Radbruch L** (2009) European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. *Palliat Med*, **23**, 581–93.
2. **Dean MM**, **Cellarius V**, **Henry B**, **Oneschuk D**, **Librach SL** (2012) Framework for continuous palliative sedation therapy (CPST) in Canada. *J Palliat Med*, **15**, 1–6.
3. **Berger JT** (2010) Rethinking guidelines for the use of palliative sedation. *Hastings Centre Rep*, **40**(3), 32–8.
4. **Kirk TW**, **Mahon MM**; **the Palliative Sedation Taskforce of the National Hospice and Palliative Care Organization Ethics Committee**. National Hospice and Palliative Care Organization (NHPCO) position statement and commentary on the use of palliative sedation in imminently dying terminally ill patients. *J Pain Symptom Manage*, **39**(5), 914–23.
5. **Maltoni M**, **Scarpi E**, **Rosati M** *et al*. (2012) Palliative sedation in end-of-life care and survival: a systematic review. *J Clin Oncol*, **30**(12), 1378–83.
6. **Boston P**, **Bruce A**, **Schreiber R** (2011) Existential suffering in the palliative care setting: an integrated literature review. *J Pain Symptom Manage*, **41**, 604–18.
7. **De Graeff D**, **Dean M** (2007) Palliative sedation in the last weeks of life: a literature review and recommendations for standards. *J Palliat Med*, **10**(1), 67–85.

8. **Rodrigues P**, **Crokaert J**, **Gastmans C** (2018) Palliative sedation therapy for existential suffering: a systematic review of argument-based ethics literature. *J Pain Symptom Manage*, **55**(6), 1577–90.
9. **Bush SH**, **Grassau PA**, **Yarmo MN**, **Zhang T**, **Zinkie SJ**, **Pereira JL** (2014) The Richmond Agitation-Sedation Scale modified for palliative care inpatients (RASS-PAL): a pilot study exploring validity and feasibility in clinical practice. *BMC Palliat Care*, **13**, 17–25.
10. **Maltoni M**, **Pittureri C**, **Scarpi E** *et al.* (2009) Palliative sedation does not hasten death: results from a prospective multicentre study. *Ann Oncol*, **20**, 1163–9.
11. **Maltoni M**, **Miccinesi G**, **Morino P** *et al.* (2012) Prospective observational Italian study on palliative sedation in two hospice settings: differences in casemixes and clinical care. *Support Care Cancer*, **20**(11), 2829–36.
12. **Maeda I**, **Morita T**, **Yamaguchi T** *et al.* (2016) Effect of continuous deep sedation on survival in patients with advanced cancer (J-Proval): a propensity score-weighted analysis of a prospective cohort study. *Lancet Oncol*, **17**, 115–22.
13. **Beller EM**, **Van driel ML**, **Mcgregor L** *et al.* (2015) Palliative pharmacological sedation for terminally ill adults. *Cochrane Database Syst Rev*, **1**, CD010206.
14. **Maltoni M**, **Pittureri C**, **Scarpi E** *et al.* (2009) Palliative sedation does not hasten death: results from a prospective multicentre study. *Ann Oncol*, **20**, 1163–9.
15. **Rietjens JA**, **van Zuylen L**, **van Veluw H** *et al.* (2008) Palliative sedation in a specialized unit for acute palliative care in a cancer hospital: comparing patients dying with and without palliative sedation. *J Pain Symptom Manage*, **36**, 228–34.
16. **Morita T**, **Chonone Y**, **Ikenaga M** *et al.* (2005) Efficacy and safety of palliative sedation: a multicenter, prospective, observational study conducted on specialized palliative care units in Japan. *J Pain Symptom Manage*, **30**(4), 320–8.
17. **Sykes N**, **Thorns A** (2003) Sedative use in the last week of life and the implications for end of life decision making. *Arch Intern Med*, **163**(3), 341–4.
18. **Morita T**, **Tsunoda J**, **Inoue S** *et al.* (2001) Effects of high dose opioids and sedatives on survival in terminally ill cancer patients. *J Pain Symptom Manage*, **36**, 228–34.
19. **Materstvedt LJ**, **Clark D**, **Ellershaw J** *et al.* (2003) EAPC Ethics Task Force: euthanasia and physician-assisted suicide: a view from an EAPC Ethics Task Force. *Palliat Med*, **17**, 97–101.
20. **Cherny N** (2009) The use of sedation to relieve cancer patients' suffering at the end of life: addressing critical issues. *Ann Oncol*, **20**, 1153–5.
21. **Levy MH**, **Cohen SD** (2005) Sedation for the relief of refractory symptoms in the imminently dying: a fine intentional line. *Semin Oncol*, **32**, 237–46.
22. **Quill TE**, **Dresser R**, **Brock DW** (1997) The rule of double effect—a critique of its role in end of life decision making. *N Engl J Med*, **337**, 1768–71.
23. **Vissers KC**, **Hasselaar JG** (2010) Palliative sedation: need for consensus guidelines and standards. *Arch Intern Med*, **170**(5), 494–5.
24. **Canadian Society of Palliative Care Physicians** (2017) *Statement on Continuous Palliative Sedation Therapy*. https://www.cspcp.ca/wp-content/uploads/2017/11/CSPCP-Statement-CPST-FINAL.pdf

Chapter 21

Radiation therapy: advancing technologies

Crystal Hann, Anand Swaminath, and Jonathan Sussman

Attitude

To enable each learner to:

- Recognize the broad scope of practice in palliative radiation oncology.
- Recognize the impact of technologic developments in radiation oncology on the patient treatment experience.
- Demonstrate appropriate understanding of the utility of palliative radiation and the importance of collaborative decision-making.

Skills

To enable each learner to:

- Demonstrate an understanding of the appropriateness of a radiation oncology referral and the implications of shared palliative care.
- Work effectively to advocate for benefit of palliative radiation in selected patient groups.
- Apply the principles of professionalism and communication in a collaborative care model.

Knowledge

To enable each learner to:

- Identify indications of palliative radiotherapy in the setting of intracranial metastatic disease.
- Identify the benefits of palliative radiotherapy in the setting of bone metastatic disease.
- Identify the role for stereotactic body radiotherapy (SBRT) in the treatment of liver metastasis.
- Understand symptoms related to radiation-associated toxicity, as well as approaches to management.

Introduction

Radiation therapy represents an important palliative modality to address pain and symptom issues in patients with advanced and metastatic cancer.[1] Approximately one-half of all radiotherapy treatments are given with palliative intent.[2] The goal of palliative radiotherapy is to use short treatment schedules to provide symptom relief that is effective and durable (within the context of overall prognosis), while minimizing toxicity.[3]

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The basic mechanism of radiation effect is to damage cellular deoxyribonucleic acid (DNA), which will lead to cellular death based on the differential repair mechanisms of tumour (low) versus normal tissue. As damaged cells attempt division, non-repaired DNA will lead to apoptosis and cell death. This, in turn, will result in shrinkage of tumour (or slowing of progression), while relatively sparing surrounding normal tissue.[4] Some surrounding tissue will be affected by radiation, leading to toxicity in the short (acute) term, generally inflammatory in nature, which can be managed with supportive care. Radiation therapy is most often delivered using an external beam of high-energy photons, generally produced by a linear accelerator. Occasionally, radiation is delivered using brachytherapy, which uses a device to bring the source of radiation in close contact with the area to be treated either on the surface, within tissue, or most commonly within a body cavity. This technique is most often used in oesophageal, lung, and gynaecological cancers.[5] Finally, radioactive isotopes can be directly injected intravenously that have affinity for specific tissues, such as thyroid and bone, and deposit the radiation locally at a fairly high dose, while sparing surrounding tissues.[6]

The scope of practice of palliative radiation oncology has changed dramatically over the past decade of clinical practice. Technologic advances have improved the ability of radiation oncologists' to treat palliative patients with reduction in toxicity. Treatment decisions for the palliative patient are now more complex, requiring a collaborative care approach to management, as well as a common understanding around the expected outcomes of radiation treatment.

Case 21.1

R.H. is a 59-year-old communications manager who was diagnosed 18 months ago with locally advanced breast cancer involving the left breast. She underwent neo-adjuvant chemotherapy, followed by lumpectomy and local radiation to the left breast. Overall, she tolerated treatment well and continued in the adjuvant setting with 1 year of targeted therapy in the form of Herceptin® for human epidermal growth factor receptor 2 (HER2)-positive disease. Her medical oncologist sees her every 6 months.

During a recent follow-up visit with her oncologist, R.H. complains of intermittent numbness involving her right hand and arm. This is beginning to affect her writing ability and she is quite concerned. The oncologist, who was concerned about the potential of metastatic disease, ordered further tests. R.H. is becoming increasingly anxious about her symptoms when magnetic resonance imaging (MRI) of the brain is ordered.

Question 1. What are the current clinical issues that need to be addressed for R.H.? How do you best support her anxiety while awaiting the test results?

The priority clinically, based on the patient's presentation, is organization of neurological imaging. This could initially involve an axial computed tomography (CT) scan to rule out metastasis or a superimposed aetiology, followed by the likely need to proceed to MRI. Breast tumours overexpressing HER2 account for 15% of breast cancers.[7] These women have been identified as having a higher risk of central nervous system (CNS) parenchymal disease relapse. CNS tumours have a major impact not only on patient survival, but also on their quality of life.[8]

The brain is a common site of metastatic disease in advanced breast cancer. Brain metastases are reported to occur in 20–40% of cancer patients, with the most common primary sites being the lung, breast, and gastrointestinal tract.[9] Presenting symptoms include headache, focal weakness, behaviour change, changes in speech and vision, seizures, and decreased level of consciousness. The development of brain metastasis is generally associated with survival of 3–6 months,

on average, although patients with limited disease (fewer than three lesions), good performance status, and otherwise controlled systemic disease may have a better prognosis. Control of brain metastases with radiation therapy will contribute to survival and reduction in the development of disability associated with neurological compromise.[10] The goal of radiation treatment is to provide relief of neurological symptoms and prevention of progression leading to further disability.

The incidence of CNS metastases is currently increasing in diseases such as breast cancer due to improved patient survival attributed to new systemic treatment options. Currently, about 20–45% of patients with HER2-positive breast cancer will develop parenchymal metastases.[7] The incidence is particularly high and remains high in patients having received Herceptin® (trastuzumab). While there is a potential that patients with brain metastases may be at high risk of other synchronous extracranial sites of parenchymal disease spread, in the case of HER2-positive cancers, extracranial disease appears controlled in 50% of cases.[8]

R.H.'s situation illustrates the need for open and clear communication from the attending oncologist to the patient, as well as the potential implications a diagnosis of Stage IV disease can have upon a patient and their family.

The next steps in clinical management for this patient should include:

1. Neurologic imaging (CT and MRI head).
2. Restaging investigations to rule out extracranial disease progression.
3. Consideration of supportive care involvement to help with the patient's anxiety and coping responses.

Case 21.1 (continued)

Diagnostic work-up

Over the course of the next 10 days, R.H. completes both a CT scan and MRI of the brain. Findings on MRI confirm the presence of three intracranial supratentorial lesions consistent with metastases. The largest lesion is in the left parietal brain and is associated with mild vasogenic oedema, measuring approximately 2.5 cm x 3.0 cm. R.H. has improved symptomatically since starting dexamethasone.

Question 2. Who needs to be involved with R.H. at this stage and why?

At this point in time, diagnostic tests have confirmed the presence of brain metastases. There are usually two main considerations in terms of decisions around management for metastatic disease:

1. Is the patient a surgical candidate?
2. Should the patient be referred to a radiation oncologist?

Surgical candidacy is usually determined by a neurosurgeon and involves the following factors:

1. Is the lesion solitary or are there multiple?
2. Is the lesion(s) causing mass effect or obstructive hydrocephalus?
3. Is there a pre-existing tissue diagnosis?

Generally, patients with larger lesions (>4.0 cm) that are resulting in mass effect are considered for surgery.[11] Otherwise, patients should be referred for radiation oncology opinion.

Question 3. What happens during the first consultation with a radiation oncologist?

During a first consultation with a radiation oncologist, the team will take into consideration tumour factors, such as histology and anatomic location, as well as patient factors, such as symptom burden and prognosis, to determine if treatment is appropriate and which approach is the most feasible. As radiation therapy is a local treatment, the goal is to treat the tumour and spare as much surrounding normal tissue as possible. This is of particular importance in the brain.

This requires careful planning with imaging that can include fluoroscopy (most often used for easily visualized bone lesions) or CT/MRI scanning if advanced three-dimensional planning is required, which is most often the case for disease in most body locations. To optimize safety and efficacy, immobilization is required to ensure accuracy of dose delivery. This may require the use of special devices to help patients maintain the optimal treatment position. In general, to receive radiation treatment, a patient must be able to lie comfortably, unattended for approximately 15 minutes. This can sometimes present a challenge for patients who have severe pain, delirium, or significant orthopnoea and may require additional pain management or procedural sedation, in collaboration with the palliative care team. Patients requiring an immobilization mask (head and neck and brain) may experience claustrophobia and this should be anticipated. Once planning is completed, treatment is delivered using a schedule that balances treatment effect with patient factors. In general, palliative treatments are given over a small number of treatments (fractions), usually between one and ten, delivered on a daily basis. Each treatment takes approximately 5–15 minutes to deliver, depending on complexity. As radiation therapy is a local treatment, side-effects depend on the area of the body being treated and the sensitive tissues that will receive sufficient dose to develop acute effects, which are self-limited and generally resolve within 2 weeks. Management of side-effects is generally supportive. Most patients who receive radiation will experience fatigue that can last for a number of weeks after treatment completion.

Question 4. How is the role of stereotactic radiotherapy (SRS) decided versus whole brain radiation?

For the past two decades, the standard of care for treatment of brain metastases has involved whole brain radiotherapy.[11] Even for those patients who were felt to be surgical candidates, whole brain radiotherapy was recommended to follow surgery for optimized control of intracranial disease. In circumstances with otherwise favourable disease parameters, whole brain radiation, offered over 5–10 fractions, was the standard recommended for patients with reasonable performance status. Acute side-effects of whole brain radiation generally include:

1. Alopecia.
2. Low-grade headache or nausea.
3. Fatigue.

Recovery from whole brain radiation can take up to 4 weeks in most patients. Whole brain radiation has also been shown to result in decline in cognition over time, specifically short-term memory, that has significant consequences on quality of life following treatment.[12]

More recently, with the advent of radiosurgery, patients with three or fewer brain metastases are considered for stereotactic brain radiosurgery. A recent trial has demonstrated more favourable outcomes with the use of high-dose, short-course, focused radiation therapy that involves 1–3 treatments to the known lesions, compared with traditional palliative whole brain radiation treatment.[10] There appears to be less acute and later toxicity when a more focused approach is used.

The toxicity of whole brain radiation can have significant adverse longer-term effects on quality of life. It would appear that the best management strategies to avoid these effects are to avoid whole brain radiation therapy. While upfront control rates of known sites of metastases appear superior with SBRT, there is a higher likelihood of subsequent development of further brain metastases in areas outside the high-dose area (i.e. the rest of the untreated brain), necessitating further treatment. One unique late effect of SBRT is brain necrosis in the treated area that has received the high dose, that can manifest as worsening of neurological symptoms and may require surgical intervention if severe. This is estimated to occur in less than 5% of patients treated with SBRT.

Question 5. Is there a situation when palliative brain radiation would not be considered?

Situations where palliative radiation may not be considered include:

1. Patients with a poor prognosis or uncontrolled symptomatic systemic disease. In this population, symptomatic treatment with corticosteroids alone is associated with progression-free survival of 1–2 months.
2. A small subset of patients who are being treated with therapies involving small molecules that are known to cross the blood–brain barrier such as the tyrosine kinases used in lung cancer and the newer immunotherapies. In these cases, in patients who are not experiencing significant symptoms and who are not otherwise progressing, radiation therapy may be reserved for progression. Early consultation with radiation oncology is still suggested to enable early intervention, if necessary, when progression occurs on systemic therapy.

Decision-making around treatment of brain metastases is becoming increasingly complex and requires multidisciplinary input, including medical oncology, radiation oncology, neurosurgery, and palliative care.

After a discussion of the pros and cons of treatment, as well as of the different techniques, R.H. elects to have treatment with stereotactic radiosurgery. Whole brain radiotherapy remains an option for future management, if required, after SRS for disease progression. Her CNS radiation team every 3 months post-SRS with MRI scans of the brain will follow R.H.

Case 21.1 (continued)

R.H. continues to do well clinically and has not been found to have any sites of metastatic disease outside the brain at the time of her brain metastases being discovered. She continues moving forward with routine clinical follow-ups with both her medical and radiation oncology teams.

Approximately 11 months after completing SRS treatment to the brain, R.H. develops new-onset back pain. The pain is not particularly bothersome but is persistent and quite different than anything she has previously experienced. R.H. reports to her oncologist that the pain is worse with walking and is relieved a little with sitting. The pain has recently started to keep her up at night. She has tried both acetaminophen and ibuprofen, with some benefit. She has no weakness, reports no change in her bowel or bladder function, and does not report any new neurological symptoms such as paraesthesiae. Physical exam is unremarkable, aside from some tenderness to palpation over the lower lumbar area.

Initial investigations include a plain X-ray of the spine that demonstrates mixed sclerotic/lytic changes in the L4 vertebral body, suspicious for metastases. A bone scan demonstrates uptake in the L4 vertebral body, as well as in the ribs, right proximal femur, and pelvis, consistent with bone metastases. Further staging investigations, including a CT scan of the chest, abdomen, and pelvis, reveal a new hypoechoic lesion in segment 6 of the liver, also concerning for metastatic disease.

Question 6. What are the radiotherapy options for management for bony metastatic disease?

The skeleton is a common site of metastases in a number of cancers, including breast cancer.[13] In most cases, there are multiple sites affected at the time of discovery, typically found on bone scanning. Palliation using radiation therapy is directed at managing pain and, in some cases, preventing progression that could lead to further pain and disability and helping sterilize the site to facilitate bone healing in cases associated with pathological fracture. Even with incomplete response, radiation can help with managing pain relief and reducing the side-effects associated with escalating doses of opioids that would otherwise be required to manage pain.

Radiation therapy for bone metastases represents a significant workload in a radiotherapy department. Palliative treatments comprise up to 40% of the total courses of radiation delivered. Palliative radiation can achieve beneficial pain response in 60–70% of patients. Complete pain response is reported to occur in less than 25% of cases. The median time for pain response is approximately 2–3 weeks, regardless of the radiation treatment regime used, with a median duration of pain relief of between 3 and 4 months. Typical courses of radiation for bone metastases include a large single treatment (800 cGy in one fraction) or a more prolonged treatment over 5–10 daily treatments (1–2 weeks). Studies comparing different regimes have demonstrated similar initial responses, with a suggestion that the duration of response is longer and the need for re-treatment less in cases where the longer courses are utilized.[14] The decision regarding the optimal fractionation approach balances the need to deliver prompt pain relief with minimal toxicity and inconvenience and will take into account performance status, comorbidities, and short-term goals of care. In general, patients who have a more favourable prognosis are offered a more protracted course of radiation therapy to support a longer duration of control and a lower need for re-treatment. Those with a poor prognosis (generally less than 3 months) are most often treated with a single fraction to support quality of life.[15] Re-treatment is generally possible after either a single or multiple course treatment, generally not sooner than 4 weeks after the initial course, given the consistent findings of equivalent upfront pain response, regardless of the fractionation used.

Question 7. What are the anticipated side-effects associated with palliative radiation for bone metastases?

The most common side-effects of radiation treatment to the bone involves a phenomenon called a pain flare, described as an increase in pain by at least 2 points using a validated pain score, with no decrease in analgesic use. This can occur in up to 40% of treatments and usually manifests within a few hours of initial treatment and can last for a few days.[16] Management includes an increase in pain medication and occasionally the addition of a short course of corticosteroid, such as dexamethasone, given that the hypothesized mechanism includes an acute inflammatory response and local oedema. The benefits of corticosteroid use in association with palliative radiation were supported by the recent SC-23 clinical trial.[17]

Other acute toxicities are site-specific and generally confined to treatment of axial sites and depend on which organs at risk are likely to receive a significant dose of radiation. In the cervical and upper thoracic spine, this can include dysphasia from oesophagitis, while in the thoracic and lumbar spine, nausea and vomiting are possible from a dose to the upper abdominal organs (stomach, liver, and small bowel). In the lower lumbar and pelvic areas, diarrhoea can occur as a result of radiation enteritis of the lower small bowel and colon.

In situations where patients present with more diffuse bony metastatic disease, there are further options for palliative radiotherapy that involve the use of radionuclide therapy or larger hemi-body radiotherapy fields.[18]

Hemi-body radiation or wide-field radiation therapy is a further technique occasionally used in palliative radiation. This technique is typically reserved for patients with diffuse and multiple painful bone metastases. A hemi-body radiation is usually delivered to either the upper half or the lower half of the body. Single-fraction hemi-body radiation has been shown in retrospective and prospective phase I and II studies to provide pain relief in 70–80% of patients. Pain relief is rapid and apparent within 24–48 hours. This is suggestive that the cells of the inflammatory pathway may be the initial target tissue, since tumour cell activities are less likely to be halted so quickly. Toxicities include minor bone marrow suppression and gastrointestinal side-effects such as nausea and vomiting in upper abdominal radiation. Pulmonary toxicity is minimal, provided the lung dose is limited to 6 Gy.

In most men with metastatic castration-resistant prostate cancer—prostate cancer that no longer responds to hormone therapy—the cancer spreads (metastasizes) to the bones. Bone metastases can cause intense pain, weakness, and bone fractures, greatly impairing quality of life—and, in some cases, causing death. Several drugs have been approved by the Food and Drug Administration (FDA) to prevent pain and fractures in patients with bone metastases, but none of these drugs improve the survival of men with prostate cancer.

Radium-223 dichloride (radium-223) is a radioactive isotope that emits low levels of alpha particle radiation. Alpha particle radiation causes double-strand breaks in DNA, killing cells. Radium-223 is a 'calcium mimetic' that, like calcium, accumulates preferentially in areas of bone that are undergoing increased turnover such as areas where bone metastases are forming. Once the drug, which can be given intravenously, reaches bone, it emits very low levels of radiation that travel less than 100 microns, or approximately four one thousandth of an inch, limiting damage to the surrounding tissues. Results from a phase III trial called ALSYMPCA show that radium-223 dichloride improved overall survival in men with advanced prostate cancer that has spread to their bones, compared with a placebo.[19]

Question 8. What is the role of radiation in the treatment of pathologic or impending fractures?

In this setting, radiation therapy has two roles:

1. Post-operatively following surgical management.
2. To enable tumour regression and provide pain relief, and for bone healing in cases where surgical management is not indicated (particularly in the ribs, shoulder, and pelvic bones).

It is widely accepted that patients at high risk of pathologic fracture and with reasonable life expectancy should undergo prophylactic orthopaedic fixation. In the case of pathologic or impending fractures, radiation can provide pain relief and tumour control but has not been shown to restore bone stability. Post-operatively, radiotherapy is usually recommended after surgical stabilization of a pathologic fracture to prevent further growth of the tumour and promote remineralization.[14]

Case 21.1 (continued)

Following palliative treatment for the lumbar spine, R.H. also has palliative treatment to the right proximal femur, as the lesion is felt to be at low risk of pathologic fracture when reviewed by orthopaedics. Follow-up imaging 3 months post-radiation shows improved mineralization of the bone within the right proximal femur.

R.H. goes on to receive palliative chemotherapy and has good response, based upon symptoms and imaging. Unfortunately, however, the lesion within segment 6 of the liver appears to show early signs of progression on CT. R.H. is re-referred to a radiation oncologist specializing in stereotactic body radiotherapy to determine if she is a candidate for treatment for her liver metastasis.

Question 9. What is the role of radiation in the management of liver metastases?

Extracranial metastases refer to metastatic cancer spread outside of the brain, most commonly to visceral organs such as the lung and liver, as well as bone. Most patients who present with extracranial metastases are treated either with systemic therapy or with palliative radiation to relieve symptoms of pain, bleeding, or obstruction. However, in the last 10–15 years, there has been increasing interest in delivering locally ablative doses of radiation to sites of extracranial metastases, with the goal of prolonged disease control and potentially to improve overall outcomes, including delay of disease progression, and long-term survival. This has been achieved historically with surgical resection (metastatectomy) where several large non-randomized studies have shown that patients who have lung and liver metastatectomies (for a wide variety of cancer types) have the potential for long-term control following complete resection of their disease. However, many patients are not candidates for surgery due to medical conditions or prefer less invasive options to treat their metastatic disease. In large part due to technological advancements in radiation oncology over the last decade, a technique known as SBRT has developed, which now permits the delivery of extremely high doses of radiation directed at extracranial targets, while simultaneously allowing for a rapid fall-off in dose around the targets in order to minimize damage to normal tissues. SBRT has been tested in the lung, liver, and other sites of metastatic disease and has been shown to be safe and effective at controlling individual sites of metastatic disease.[20]

Question 10. In what situations would you consider offering SBRT in the treatment of extracranial metastases?

The most common situation to consider SBRT is in the setting of oligometastatic disease. First coined by Hellman and Weischelbaum in 1995, oligometastatic disease refers to an intermediate state between localized and widespread cancer where metastases are concentrated to a few, or limited, sites.[21] The theory behind the treatment of oligometastases was that if one could eradicate all known sites of metastatic disease, then this has the potential to delay progression, and possibly cure patients who were once thought to have incurable disease. SBRT has been most commonly studied in this setting, and several pilot studies in breast, lung, and colorectal cancers have shown that SBRT may delay progression (compared to historical series of palliative radiation and/or systemic therapy alone) and improve long-term survival. The results of recent randomized trials demonstrating benefit both in disease control and in survival time have created enormous interest in further evaluating SBRT, and as a result, several large-scale randomized trials in lung, prostate, breast, and multiple cancers are ongoing and will hope to definitively affirm the role of SBRT in oligometastatic disease.

Despite these promising early results, several questions still remain unanswered and should be considered when selecting appropriate patients for oligometastatic SBRT. The first question is how many metastases should be treated. The trials have typically shown that SBRT is effective for up to five individual metastases (considered the benchmark), but others have suggested an

upper limit of three lesions to be more appropriate. Another issue is how long after the original cancer diagnosis (or previously controlled cancer) SBRT should be considered (i.e. the disease-free interval). Leaning on previous radiation and surgical studies, it would appear that the longer, the better and that a disease-free interval of at least 6 months to 1 year from original treatment would result in a larger chance of benefit from SBRT than less than 6 months. A third question is what the maximum size is of any individual metastasis that would be treatable. This largely depends on the location of the lesion in relation to other normal tissues, but a typical rule-of-thumb is a maximum lesion size of 5 cm (although larger lesions can be treated, if able to do so safely). A final question is what other patient factors need to be considered. This can vary, depending on cancer type, but in breast cancer, for example, such factors as hormone receptor-positive status, bone only versus bone + visceral disease, and HER2-positive disease all may increase the chances of efficacy for SBRT.

In this particular case, one could consider SBRT for the liver metastasis, so long as the disease has been controlled for at least 6 months and the lesion in the liver is not too large and not adjacent to any normal tissues that would make SBRT too risky, and that there is a plan for further systemic therapy following SBRT in order to control the other sites of metastatic spread.

Conclusion

In this chapter, we have illustrated common scenarios in which palliative radiation therapy may help symptom management and quality of life. Patients with established metastatic disease who are experiencing symptoms such as pain, organ dysfunction, bleeding, or obstruction that can be safely targeted with radiation therapy should be discussed with radiation oncology. Treatment decision-making has become increasingly complex and multidisciplinary case conferences (MCCs) that involve radiation oncology input can support optimal quality of care. The principles of using short courses of treatment targeting symptomatic sites that use advanced imaging and treatment delivery technologies ensure the effective use of palliative radiation therapy.

References

1. **Jones JA, Lutz ST, Chow E, Johnstone PA** (2014) Palliative radiotherapy at the end of life: a critical review. *CA Cancer J Clin*, **64**(5), 296–310.
2. **Hoegler D** (1997) Radiotherapy for palliation of symptoms in incurable cancer. *Curr Probl Cancer*, **21**(3), 129–83.
3. **Rodin D, Grover S, Elmore SN** *et al.* (2016) The power of integration: radiotherapy and global palliative care. *Ann Palliat Med*, **5**(3), 209–17.
4. **Hall EJ, Giaccia AJ** (2006) *Radiobiology for the Radiologist*, 6th edn. Lippincott Williams & Wilkins, Philadelphia, PA.
5. **Lutz ST, Jones J, Chow E** (2014) Role of radiation therapy in palliative care of the patient with cancer. *J Clin Oncol*, **32**(26), 2913–19.
6. **McEwan A** (2000) Use of radionuclides for the palliation of bone metastases. *Semin Radiat Oncol*, **10**(2), 103–14.
7. **Ono M, Ando M, Yunokawa M** *et al.* (2009) Brain metastases in patients who receive trastuzumab-containing chemotherapy for HER2-overexpressing metastatic breast cancer. *Int J Clin Oncol*, **14**(1), 48–52.
8. **Church DN, Modgil R, Guglani S** *et al.* (2008) Extended survival in women with brain metastases from HER2 overexpressing breast cancer. *Am J Clin Oncol*, **31**(3), 250–4.
9. **Tsao MN, Xu W, Wong RK** *et al.* (2018) Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev*, **1**, CD003292.

10. **Linskey ME, Andrews DW, Asher AL** *et al.* (2010) The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol*, **96**(1), 45–68.
11. **Hart MG, Walker M, Dickinson HO, Grant R** (2005) Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases. *Cochrane Database Syst Rev*, **1**, CD003292.
12. **Patchell RA, Tibbs PA, Walsh JW,** *et al.* (1990) 1990A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med*, **322**(8), 494–500.
13. **Pin Y, Paix A, Le Fevre C, Antoni D, Blondet C, Noel G** (2018) A systematic review of palliative bone radiotherapy based on pain relief and retreatment rates. *Crit Rev Oncol Hematol*, **123**, 132–7.
14. **Wu J** (2003) Cancer Care Ontario practice guidelines initiative supportive care group: meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys*, **55**, 594–605.
15. **Kachnic L, Berk L** (2005) Palliative single-fraction radiation therapy: how much more evidence is needed? *J Natl Cancer Inst*, **97**(11), 786–8.
16. **Hird A, Chow E, Zhang L** *et al.* (2009) Determining the incidence of pain flare following palliative radiotherapy for symptomatic bone metastases: results from three Canadian cancer centers. *Int J Radiat Oncol Biol Phys*, **75**(1), 193–7.
17. **Westhoff PG, de Graeff A, Geerling JI, Reyners AK, van der Linden YM** (2014) Dexamethasone for the prevention of a pain flare after palliative radiotherapy for painful bone metastases: a multicenter double-blind placebo-controlled randomized trial. *BMC Cancer*, **14**, 347.
18. **Hoskin P, Ford H, Harmer C** (1989) Hemibody irradiation (HBI) for metastatic bone pain in two histologically distinct groups of patients. *Clin Oncol*, **1**(2), 67–9.
19. **Hoskin P, Sartor O, O'Sullivan JM** *et al.* (2014) Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. *Lancet Oncol*, **15**(12), 1397–406.
20. **Chang DT, Swaminath A, Kozak M** *et al.* (2011) Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. *Cancer*, **117**(17), 4060–9.
21. **Hellman S, Weichselbaum RR** (1995) Oligometastases. *J Clin Oncol*, **13**(1), 8–10.

Chapter 22

Chemotherapy

Rachel Rudney and Paul J. Daeninck

Attitude

To enable the learner to:

- Embrace the wide variety of anti-neoplastic therapies available for patients with malignancies.
- Recognize the challenge patients and families face when discussing therapies for cancer.

Skills

To enable the learner to:

- Counsel the patient and family on the general principles and choices in the treatment of malignancies.

Knowledge

To enable the learner to:

- Distinguish between cytotoxic chemotherapy, immunotherapy, and targeted therapies.
- Recognize the adverse effects and supportive treatments for each of the above.

Case 22.1

J.S. is a 50-year-old woman of Filipino ancestry, with a past history of hypertension (on hydrochlorothiazide) and remote smoking history (12 pack years, stopped 20 years ago). She is presently working as a nurse in a personal care home in a medium-sized Canadian centre. She develops fatigue, loss of appetite, and a persistent cough over several weeks but seeks medical attention when haemoptysis develops. Investigations reveal a 3-cm mass in her right upper lobe (RUL) and an enlarged mediastinum. Bronchoscopy and mediastinoscopy discover a malignant-appearing mass and extensive lymphadenopathy of the mediastinum and carinal areas. Biopsy confirms adenocarcinoma. Her surgeon informs her of the diagnosis of lung cancer and suggests a consult with medical oncology for consideration of chemotherapy.

Question 1. What are the important factors when determining the course of treatment for lung cancer?

Lung cancer can be classified by morphological analysis into two broad fields: small cell lung cancer (SCLC) (neuroendocrine cell) and non-small cell lung cancer (NSCLC). NSCLC comprises 85% of malignancies of the lung.[1] NSCLC can be further divided into three tissue types: (1)

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squamous cell carcinoma; (2) adenocarcinoma; and (3) not otherwise specified (NOS) as adenocarcinoma or squamous cell carcinoma. Adenocarcinoma has been shown to be more prevalent in persons who have never smoked.[1] Computed tomography (CT) and magnetic resonance imaging (MRI) are used to accurately assist with initial staging and determine the extent of lymph node involvement. Histological analysis is important for defining morphology, the presence of neuroendocrine characteristics, and whether the tissue is of metastatic origin.[2] Molecular analysis is now necessary for initiation of individualized treatment, especially with identification of several therapies with specific targets.[1]

Factors important for determining prognosis include age, stage of cancer, histological findings, molecular analysis, and comorbidities. Progression and course of treatment are determined based on analysis of these factors.[3,4] Further molecular testing for specific gene mutations is standard practice and can determine suitability for use of appropriately targeted agents.[5] Staining for programmed cell death ligand 1 (PD-L1) expression is also recommended to determine cancer sensitivity to immunotherapy.[6]

Question 2. What is J.S.'s diagnosis and what stage would her disease be classified as?

J.S. is diagnosed with NSCLC adenocarcinoma. Due to the 3-cm size of the tumour and subsequent nodal involvement, J.S. presents with Stage IIIb lung cancer (see Figure 22.1) and TNM classification T2N3M0 (see Table 22.1).[3,7] This method of staging allows the oncology team to determine the best choice of therapy for J.S.

Case 22.1 (continued)

JS is seen by a medical oncologist who suggests further molecular testing of her tumour to help determine chemotherapy options. He advises J.S. that her situation is not curable, but with response to appropriate treatment, she may be able to live for several more months and possibly years. Her family asks about specific therapy options, to which the oncologist outlines a course of therapy and refers them to the clinic pharmacist for further information.

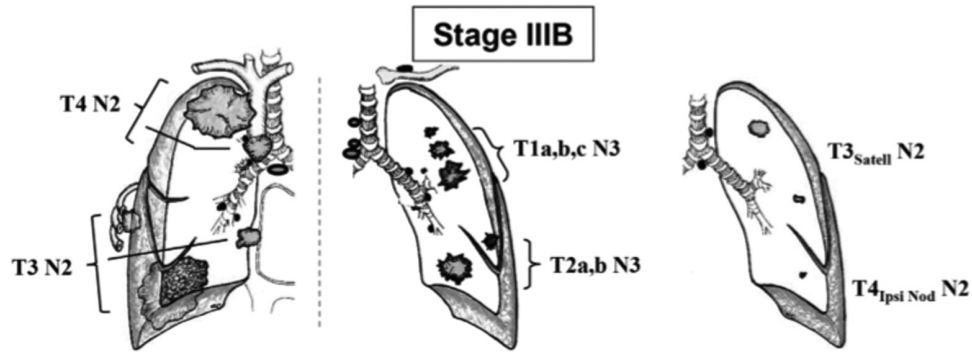


Fig. 22.1 Presentation of Stage III lung cancer.
Reproduced with permission from Detterbeck FC, et al. 'The Eighth Edition Lung Cancer Stage Classification'. *Chest*, Vol. 151, Issue 1, pp.193–203. Copyright © 2017 Elsevier Ltd.

Table 22.1 Summary of TMN staging of NSCLC based on the 8th edition of Lung Cancer Stage ClassificationSource: data from Brierley JD, Gospodarowicz MK, Wittekind C (eds.) *TNM Classification of Malignant Tumours*, 8th edition. Copyright © 2017, John Wiley and Sons.

Stage	T (Tumour)	N (Node)	M (Metastasis)
0—Carcinoma *in situ*	Tis	N0	M0
I	T1, T2	N0	M0
Iia	T1–3	N0–1	M0
IIIa	T1–3	N3	M0
	T4	N0 or N1	M0
IIIb	T1–3	N3	M0
	T4	N2 or N3	M0
IV	T1–4	N1–3	M1

Question 3. How is chemotherapy treatment classified?

Curative chemotherapy

Chemotherapy is administered with the intent of providing complete remission with no recurrence of the disease. Several types of leuakemia and lymphoma are routinely treated primarily with chemotherapy directed at achieving cure. Chemotherapy with curative intent may be given in conjunction with surgery or radiation.[4,8]

Neo-adjuvant chemotherapy

Chemotherapy treatment is used to decrease the size of the tumour(s) before surgical resection. This option is routinely offered to patients with inflammatory breast cancer and rectal cancer, as supported by clinical trial evidence. This may also be combined with radiation to achieve best surgical resection, again aimed at cure.[4]

Adjuvant chemotherapy

Chemotherapy is administered after surgical resection of the malignancy to decrease the risk of relapse of disease and increase rates of survival. It may be combined with local radiation to achieve the best outcome. Adjuvant therapy is standard practice for a number of tumour sites, including breast, colon (Stage III and high-risk Stage II), and lung (Stages II and IIIa).[4]

Maintenance therapy

Chemotherapy is administered to prevent the recurrence of cancer following remission after initial therapy. Treatment may extend for a prolonged period of time, depending on the initial diagnosis.[4] This is an integral part of some paediatric cancer treatment protocols[9] and used in adults with specific molecular findings (e.g. rituximab in lymphoma).

Life prolongation chemotherapy

Chemotherapy is provided to control the growth of cancer, manage symptoms, and extend survival without the intention to cure. This type of therapy may be given in combination with other symptom management modalities.[8]

Palliative chemotherapy

Palliative chemotherapy can be offered at first point of diagnosis or given in recurrent or advanced disease. This treatment may prolong life, but the primary intention is to improve quality of life without the intention to cure.[8]

Question 4. Molecular analysis has become routine for patients with NSCLC to identify genes for which treatments are available. What genes should be tested?

Tyrosine kinase inhibitors (TKIs) have been developed and shown in clinical trials to reduce tumour growth and prolong progression-free survival in patients having specific molecular or genetic markers. The American Society of Clinical Oncology (ASCO) has endorsed the 2018 guidelines put out by the College of American Pathologists (CAP), which recommend testing for *EGFR*, *ALK*, *ROS1*, and *BRAF* gene mutations, as effective treatments for each of these are available.[5]

Case 22.1 (continued)

The oncology team reviews the molecular testing results with J.S. She has wild-type (unmutated) *EGFR* and *BRAF* genes, and an *ALK* gene rearrangement. This indicates J.S. should start therapy with a TKI targeting this mutation; crizotinib is available at her regional cancer centre. She is started at a dose of 250 mg twice a day. She experiences mild nausea, occasional diarrhoea, and visual disturbances characteristic of this agent.[10]

Tyrosine kinase inhibitors

TKIs make up a heterogeneous group of medications that have been indicated for a range of malignant diseases. These small molecules enter the cancer cell and prevent the transfer of phosphate from adenosine triphosphate (ATP) within the cell, causing tumour cell growth inhibition, preventing cellular proliferation, and inducing cellular apoptosis. More than 80 TKIs have been developed, with several undergoing clinical trials at any one time. These can be grouped into five main types, depending upon their target (see Table 22.2): vascular endothelial growth factor receptor (VEGF-R), breakpoint cluster region–abelson murine leukaemia viral oncogene homolog 1 (BCR-abl), B-cell receptor (BCR), epidermal growth factor receptor (EGFR), and anaplastic lymphoma kinase (ALK).

These therapies have greatly increased the survival of patients with NSCLC, with some patients living for several months to years longer than with conventional chemotherapy.[11] Adverse effects are generally mild to moderate (Grade 1 or 2) in intensity, affecting the skin, gastrointestinal organs, eyes, and endocrine function.[11]

Case 22.1 (continued)

J.S. is followed by her oncology team (including the pain and symptom service in her centre) every 2–3 months, and notes that her pulmonary mass and lymph nodes have shrunk over 11 months. One month later, she develops a dry cough, which, upon investigation, demonstrates recurrence of the disease in her RUL. The medical oncologist recommends a switch to cytotoxic chemotherapy.

Table 22.2 Classification of tyrosine kinase inhibitors

Class	VEGF receptor	BCR-abl	BCR	EGF receptor	ALK
Mechanism	Anti-angiogenesis	Blocks BCR-abl protein formation	Dysregulation of B-cell malignancies	Blocks cancer cell proliferation	Blocks *ALK* fusion gene activity
Representative malignancies	Renal cell carcinoma, gastrointestinal stromal tumour (GIST), hepatocellular carcinoma, thyroid cancer, pancreatic/ neuroendocrine tumours	Ph+ CML, ALL, myelodysplasia, GIST	Follicular lymphoma, CLL, SLL, mantle cell lymphoma	NSCLC, melanoma, breast cancer, thyroid cancer	NSCLC (non-smokers)
Adverse effects	Diarrhoea, skin rash	Fluid retention, nausea/vomiting	Bleeding, rash, colitis, hepatotoxicity	Diarrhoea, skin rash	Nausea and vomiting diarrhoea, hyperglycaemia, visual changes

Question 5. What kinds of chemotherapy are available?

In general, chemotherapy describes a group of medications that are aimed at disrupting the growth cycle of the cancer cell to accelerate its death. Classically, chemotherapy agents were toxic towards all cells, and thus caused a wide range of side-effects, limiting their dosage and used in only the healthiest of patients. Combining agents to take advantage of complementary mechanisms of action has created a number of acronyms well known and used within the haematology and oncology community (e.g. CHOP, ABVD, FOLFIRI, FEC-D, etc.) (see Table 22.3).[12,13]
Detailed mechanisms of action of these agents is beyond the scope of this chapter. The reader is encouraged to explore textbooks (e.g. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 11th edition, 2019)[14] or well-recognized academic or cancer centre websites (e.g. www.bccancer.bc.ca)[13] for more details.

Question 6. What chemotherapy can be offered to J.S.?

Appropriate chemotherapy at this stage of disease would be use of a doublet, e.g. cisplatin and pemetrexed combination for four cycles.[6] Following discussion with J.S. and her family, she decides to proceed with life prolongation chemotherapy. The survival rate for this stage is 7–9 % at 5 years, though advances in targeted therapies may improve these numbers in the future.[15]

Question 7. What is the advantage of offering both treatments at once?

Given that NSCLC has a 5-year survival rate of 14% across all stages, it is important to determine the right treatment options for each patient. Platinum-based doublet therapies result in an increase in survival rates and improvement in quality of life, compared to previous chemotherapy regimes for NSCLC, and have become the standard of care for patients with advanced

Table 22.3 Classification of chemotherapy

Type	Action	Examples
Class: Cytotoxic chemotherapy		
Antibiotics:		
Anthracycline-based	Inhibition of topoisomerase II	Doxorubicin, epirubicin
Non-anthracycline-based	Inhibition of DNA and RNA synthesis	
	Inhibition of DNA and RNA synthesis	Bleomycin, actinomycin D
Antimetabolites:	Interruption of DNA and RNA synthesis by substitution via naturally occurring metabolites with non-functional analogues	
Purine analogues		Mercaptopurine, cladribine, fludarabine, thioguanine
Pyrimidine analogues		5-fluorouracil, capecitabine, hydroxyurea, gemcitabine
Folate analogues		Pemetrexed, raltitrexed, methotrexate
Alkylating agents	Interruption of DNA, RNA, and protein synthesis via addition of alkyl groups	Bendamustine, mustards in general, cyclophosphamide, busulfan, chlorambucil, temozolamide
Topoisomerase inhibitors:	Initiate DNA strand breaks by interfering with topoisomerases	
Topoisomerase I inhibitors		Irinotecan, topotecan
Topoisomerase II inhibitors		Etoposides, anthracyclines, amsacrine, teniposide
Platinum agents	DNA crosslinking, preventing DNA repair, synthesis	Cisplatin, oxaliplatin, carboplatin
Taxanes	Mitotic inhibitors, disrupt microtubule formation	Paclitaxel, docetaxel
Vinca alkaloids	Prevents microtubule formation and mitotic spindle formation and inhibits cell division	Vincristine, vinblastine, vinorelbine
Class: hormonal therapy		
Androgen and oestrogen inhibitors	Inhibition of signalling through receptor antagonism	Bicalutamide, flutamide fulvestrant, tamoxifen
Aromatase inhibitors	Block conversion of androgens to oestrogens	Anastrozole, letrazole
Corticosteroids	Induction of apoptosis (haematologic malignancies)	Dexamethasone
Class: Immunomodulation		
Cytokines	Elicit immune responses via changes in cell signalling	Interferons
Immunomodulators	Inhibition of angiogenesis, enhancement of innate and adaptive immune systems	Lenalidomide, thalidomide
Class: Targeted therapy		
Monoclonal antibodies	Target specific molecules in signal transduction pathway of cancer cells	Bevacizumab, cetuximab, rituximab

(*continued*)

Table 22.3 Continued

Type	Action	Examples
Protein kinase inhibitors (see Table 22.2*)*	Interfere with signal transduction pathway of cancer cells	Erlotinib, gefitinib, sorafinib
Proteasome inhibitors	Block proteasome activity, inhibit cancer cell proliferation	Bortezomib, carfilzomib, ixazomib

Source: data from Kubiczkova L, et al. (2014). 'Proteasome inhibitors – molecular basis and current perspectives in multiple myeloma'. J Cell Mol Med, 18: 947–96112; and http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index#c-content.13

NSCLC.[15] Experimental data and meta-analysis support the continued use of a platinum agent as a doublet in combination with a third-generation agent to offer the best survival advantage.[16] Given the complexities of the tumour make-up, a multidrug system approach can provide tumour management and reduce the risk of developing drug resistance. The current approach is to proceed with four cycles of the doublet and then to assess outcomes via diagnostic imaging with CT and/or MRI. Due to the toxicity of platinum doublets, prolonging treatment for more than four cycles has been shown to increase the burden of symptoms and side-effects, while not increasing survival.[15]

Question 8. What are some of the side-effects associated with cisplatin and other platinum-based chemotherapies? How would we manage them?

Platinum-based compounds work through the binding of nuclear deoxyribonucleic acid (DNA), proteins, and peptides in cancer cells. This, in turn, leads to apoptosis and a decrease in cell numbers. Due to the fact that platinum compounds cannot readily distinguish malignant cells from healthy cells, significant cytotoxicity will be seen in body systems with a higher cell turnover.[17]

Nephrotoxicity

Acute renal failure and hypomagnesaemia account for the majority of side-effects due to damage of the proximal tubules.[18] Management of nephrotoxicity includes hyperhydration prior to treatment, prolonged infusion times, and supplements to counteract the loss of magnesium.[17]

Neurotoxicity

Sensory neuropathy of the peripheral nervous system, including paraesthesiae, myasthenia, and dysesthesia, is the main adverse effect of cisplatin. The areas primarily affected are the hands and feet, but the pharynx and larynx may be involved as well. Symptoms may be acute and resolve post-therapy, or be chronic and persist for years following treatment. No clear preventative agent is available for these symptoms, and onset is usually followed by a reduction of dose or discontinuation of therapy. Ototoxicity may also result from direct nerve damage or cochlear hair cell damage from reactive oxygen formation.[19]

Gastrointestinal toxicity

Nausea and emesis are the primary gastrointestinal symptoms resulting from treatment with platinum compounds. More than 90% of patients will experience vomiting without effective anti-nausea

therapy. Cachexia, significant weight loss, and significant fatigue may result if untreated. Treatment with doublet antiemetic protocols[18] can reduce the impact of acute nausea and emesis, and triplet therapy can also help to significantly reduce the occurrence of delayed nausea and vomiting.[18]

Bone marrow suppression

Isolated anaemia is a well-known side-effect to single-agent cisplatin use, but when combined with another agent, all three cell lines may be affected.[19] This can be manifested by malaise, fatigue, and weakness. Significant neutropenia puts patients at risk of febrile illness, and regular screening of complete blood count and absolute neutrophil count (ANC) should be carried out. Due to the high risk of infection, patients who present with febrile neutropenia (temperature over 38°C) should seek immediate medical attention.

Question 9. What are the side-effects associated with pemetrexed and how would we manage them?

Pemetrexed is a folate antagonist that has shown efficacy in the treatment of NSCLC, as part of a doublet in second-line or maintenance therapy.[15] It is better tolerated than other folate antagonists, but side-effects should be discussed with the patient.

Myelosuppression

This is particularly prevalent in patients receiving doublet therapy. As above, education for the patient to recognize febrile episodes and emphasizing the importance of seeking medical assistance when they occur. Repeated episodes may cause dose adjustment of subsequent cycles.

Nausea and vomiting

As per above, this can be controlled with appropriate use of antiemetics.

Mucositis

This is seen in about 15% of patients and can be treated with oral rinses and good mouth care. Painful lesions are not common but may require a short course of oral analgesics.

Fatigue

This is common with many kinds of chemotherapy and may be helped with energy conservation practices and attention to daily activity. Patients who are more active (exercise included) may experience less of this side-effect.

Rash

This may take the form of desquamation, dermatitis, or rarely erythema multiforme (less than 1% occurrence). Topical corticosteroid creams are recommended if the patient is very symptomatic.

Case 22.1 (continued)

J.S. completes four cycles of doublet therapy, followed by CT imaging that demonstrates an excellent response (90% reduction in primary tumour and size of lymph nodes). She then is started on maintenance therapy using pemetrexed.

Question 10. What is maintenance treatment and why would we not offer more of the initial treatment?

Maintenance therapy

This is a treatment to keep a malignancy from progressing or returning. It consists of treatment with chemotherapy drugs or other anti-tumour agents (e.g. monoclonal antibodies). If a favourable response is achieved with NSCLC chemotherapy, it may be beneficial to proceed with non-platinum compound maintenance therapy. Continuing with a first-line platinum agent is not recommended, based on data showing that longer use of platinum agents is associated with an increasing burden of neuropathic symptoms and no further increase in survival.[20] Pemetrexed was shown to increase survival of non-squamous NSCLC patients by 5 months, compared to the placebo group, following first-line treatment.[20] The ease of administration (10-minute infusion time) and the low risk of adverse side-effects make pemetrexed a good choice for maintenance therapy for J.S.[15]

Case 22.1 (continued)

Four months later, CT imaging shows recurring growth of J.S.'s cancer and new lesions in her liver. The oncology team suggests the use of immunotherapy in an effort to control its growth. They propose starting it next week if she and her family are in favour.

Question 11. What is immunotherapy and what benefits/adverse effects can J.S. expect?

Immunotherapy has dramatically changed outcomes for some cancer patients who were previously faced with few (if any) treatment options. The identification of agents active against the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) or programmed cell death 1 (PD-1) immune checkpoint has resulted in durable remissions for some patients facing certain death from advanced malignancies. Although the treatment themselves are well tolerated and do not carry the same stigma for patients as standard chemotherapies (e.g. alopecia, nausea/vomiting, and profound fatigue), significant and serious side-effects can occur, usually presenting as immune-mediated reactions.[21]

These compounds, belonging to the class of monoclonal antibodies, target CTLA-4 and PD-1 (and its ligand, PD-L1), receptors found on the surface of T-cells. Normally, T-cells provide immune surveillance, searching for and destroying cells recognized as foreign. Malignancies can block access to these receptors, preventing antigen-presenting cells (dendritic cells) from priming T-cells. Once blocked, T-cells will not target the malignancy, which allows for unchecked cell growth and migration. When these agents are employed, the immune system is 'unmasked' and T-cells can fully recognize and attack malignant cells. This often results in a rapid reduction in size of the tumours, with some patients having complete and durable remissions.[22]

However, this fully activated immune system can lose the ability to be regulated and normal healthy tissue can become a target. The full spectrum of organs affected and associated manifestations can be seen in Figure 22.2.[21] Oncologists using these agents are continuously alert for the possibility of immune-mediated reactions, which are easily treated with steroids (prednisone 1–2 mg/kg/day) when caught early.[23]

With many clinical trials under way at the time of writing of this chapter, the number of tumour types responding to this class of therapy will certainly increase. As of 2019, malignancies approved by Health Canada for immunotherapy include advanced melanoma, advanced NSCLC, renal cell carcinomas, bladder cancers, squamous cell cancers of the head and neck, and Hodgkin's lymphoma. The available agents (2019) can be divided along specific targets.

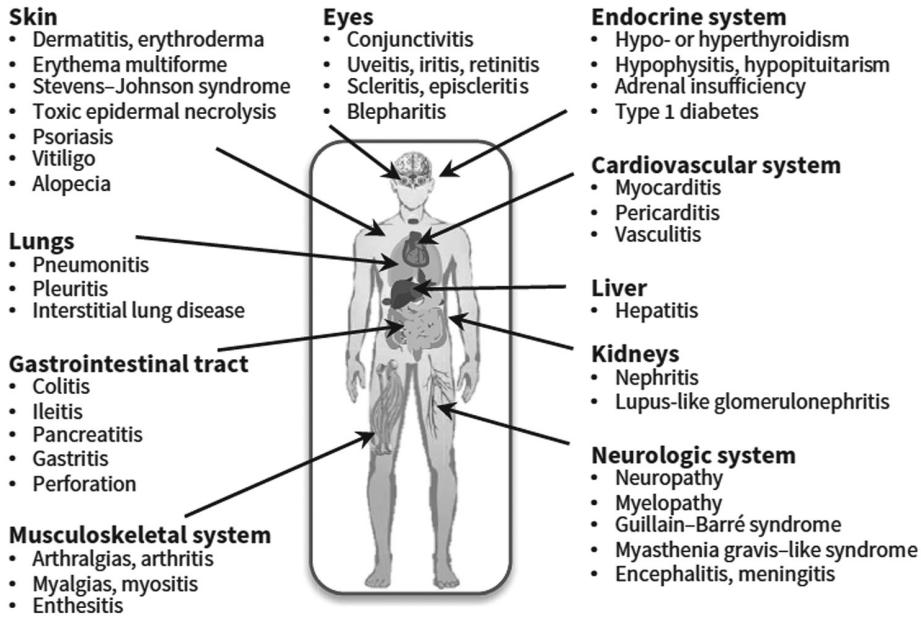


Fig. 22.2 Possible organs affected by immunotherapies.
Reproduced with permission form Esfahani K, et al. 'Adverse events associated with immune checkpoint inhibitor treatment for cancer'. *Can Med Assn J*, Vol.191, Issue 2. pp. E40–E46. Copyright © 2019. Joule Inc.20

The use of corticosteroids during treatment with checkpoint inhibitors is somewhat controversial. Most clinical trials investigating these compounds excluded patients with autoimmune disorders due to the possibility that steroids could antagonize checkpoint inhibitor activity.[24] However, steroids (prednisone, methylprednisolone) are standard first-line pharmacologic agents for treatment of immune-mediated reactions associated with checkpoint inhibitor therapy.[23] A systematic review of 27 studies did not show reduced responses or poorer outcomes for those using steroids and immune checkpoint inhibitors for haematologic or solid tumour indications.[24] A retrospective review of patients with NSCLC treated with immune checkpoint inhibitors at a single centre did not show a difference in overall survival for those using steroids for non-palliative indications, but noted a significant reduction in overall survival for those using steroids for palliative indications. The authors stated that palliative steroid use might be a marker of poor-prognosis patients, rather than a medication effect.[25] This contrasts with a review of patients whose adverse events due to immune checkpoint therapy were reported to the Food and Drug Administration (FDA) in the United States. This report did not find a reduced rate of response or duration of response related to steroid use, regardless of the reason(s) for use.[26] Given this uncertainly, palliative care providers should communicate with members of the oncology team regarding initiation of steroids for palliation of symptoms or adverse reactions, and patients should be counselled as to the benefits and potential risks of their use in this situation.

Table 22.4 Classification of checkpoint inhibitor agents (immunotherapy agents)

CTLA-4 inhibitor	PD-1 inhibitors	PD-L1 inhibitors
Ipilumumab	Nivolumab	Atezolizumab
	Pembrolizumab	Durvalamab
		Avelumab

Question 12. J.S.'s family read on the internet that some cancer centres offer bone marrow transplant or the use of vaccine therapy for patients with advanced malignancies. Is J.S. a possible candidate?

Stem cell transplantation (also known as bone marrow transplants or BMTs) is a process of infusing cytotoxic chemotherapy (or using radiotherapy) in doses high enough to kill the majority of cancer cells. However, this is toxic to the bone marrow and other cells of the body. Stem cells (usually donated but may be autologous) are infused into the patient to allow for regeneration of the marrow and reinstitution of cellular immunity. This has become standard therapy for some types of leukaemia, lymphomas, and myeloma. It can also be used for neuroblastoma in children. Although there have been attempts at using transplantation for solid tumours in the past, success rates were poor and adverse effects, including death, were unacceptably high. Research into the use of stem cells as therapy for solid tumours continues,[27] but at this time, it is not a recommended therapy for lung cancer patients.

Research continues on the use of vaccines to prevent and, in some cases, treat various cancers. Several vaccines already exist and have been shown to prevent viruses that may eventually induce malignancy. Vaccines against hepatitis B virus and human papillomavirus (HPV) have substantially reduced the rate of hepatocellular carcinoma and cervical cancers. The latter may also be effective against some types of head and neck carcinomas and anal carcinomas. A recent study estimated the worldwide prevalence of HPV-associated cancers to be 630 000 cases, and up to 90% could be prevented by universal vaccination.[28] This would significantly reduce the burden of cancer, especially in underdeveloped countries.

Vaccines have also been developed for treatment of non-viral-linked malignancies, including prostate cancer, breast cancer, melanoma, and B-cell leukaemias and lymphomas. These vaccines target oncogenic proteins (e.g. Her2/Neu), cellular expressed antigens (e.g. GP-100, Melan-A, or PSA). Human use has been restricted to clinical trials, with early but encouraging results.[29]

Adoptive T-cell therapy has been in development for several decades, mostly through lab studies, but recently translated to human use through clinical trials.[30] Stimulation of specific populations of lymphocytes (e.g. lymphocyte-activated killer cells, tumour-infiltrating lymphocytes) was demonstrated to benefit some patients with melanoma and renal cell cancers.[30] This type of cellular immunotherapy is dependent upon the antigen specificity of T-cells, which can be modified by genetic manipulation to target specific antigens expressed by tumour cells. Now known as chimeric antigen receptor T-cell therapy (CAR-T), it has been successfully used in patients with chemotherapy-resistant leukaemias (adults and children) and lymphomas, and recently in patients with glioma and pancreatic carcinoma.[31] A recent report showed CAR-T for chemotherapy-resistant lymphoma resulted in durable response rates of more than 60% over as long as 12 months.[32] This positive result has sparked interest in treatment of solid tumours and other immune-mediated conditions but remains an expensive and experimental therapy at the time of writing.[31]

Case 22.1 (continued)

J.S. completes two cycles of pembrolizumab, with excellent initial shrinkage of tumours in all locations. She continues for an additional 4 months, gaining strength and enjoying her new granddaughter. One day, she reaches into the crib and feels a sharp pain between her shoulder blades. She uses acetaminophen to reduce the pain but finds it difficult to stand or bend over. Two days later, she presents to the oncology urgent care centre. The pain is now radiating down her back and she is having difficulty with left leg weakness. The nurse

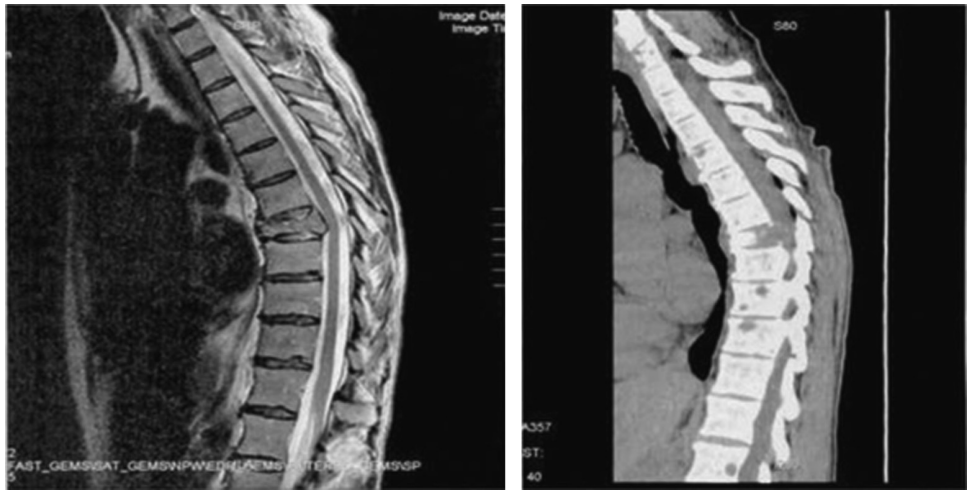


Fig. 22.3 MRI (left) and CT (right) images showing T8 compression of the spinal cord.
Reproduced with permission from Chow E, Finkelstein JA, Sahgal A, and Coleman RE, 'Metastatic Cancer to the Bone' *In* DeVita VT, Lawrence TS, Rosenberg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 11th edition. Wolters Kluwer, New York, 2018, pg 2520.

practitioner urgently orders MRI of the spine and discovers J.S. has a pathologic fracture of the T8 vertebra, with associated spinal cord compression (see Figure 22.3). She also has evidence of other bony lesions in several thoracic and lumbar vertebrae.

Question 13. Why did J.S. develop spinal cord compression? What are the presenting symptoms and signs?

Primary lung cancer may present initially with spinal cord compression or as a later symptom of metastatic spread. The tumour cells may invade through the spinal dural or medullary layer directly, or through the circulation via the spinal arteries or intraspinal veins.[33] Spinal cord compression is seen in 2.5–5% of cancer patients and is considered a medical emergency.[33,34] The first symptoms include increasing back pain at the compression site or the general area and lost/reduced sensation in the areas below the site of compression. This pain may be the result of direct nerve impingement or compensation due to instability or fracture of the vertebrae.[33] Posterior protrusion of the vertebrae and invasion of cancer leads to arterial, venous, and neural impingement and may result in dysesthesia and/or neuropathic pain in the lower limbs.[33] Bowel and urinary changes indicate progressive disability and should be treated urgently. Clinical outcomes are improved with timely intervention, but full recovery of mobility after the onset of motor symptoms is distinctly uncommon.[35]

Treatment for spinal compression involves a collaborative approach involving oncology, radiology, surgery, and palliative care, depending upon the patient's preference for the type of intervention.[33,35] Acute treatment should include corticosteroid administration followed by diagnostic imaging (X-ray and magnetic resonance) to determine the site and extent of the damage. Surgical decompression is the preferred method of treatment, but patients who cannot tolerate surgery are treated with corticosteroids, analgesics, and palliative radiotherapy (see Chapter 21 for further details) to reduce the burden of symptoms.[33,35]

Case 22.1 (continued)

J.S. is very disappointed that the cancer has progressed and opts for radiotherapy only to help with the pain. The medical oncologist advises her that further chemotherapy will not change the outcome, given the extent of the progression. She and her family meet with the palliative care team while in hospital, and plans are put in place for her to stay home until her death, which happens in approximately 3 months. She was able to enjoy her last summer with her family in attendance.

When all chemotherapy options for patients with NSCLC have been exhausted, the focus should be on continued symptom management and ensuring quality of life. The most common symptoms for these patients include dyspnoea, pain, fatigue, and anorexia (management of these are found elsewhere in this book).

References

1. **Gridelli C, Rossi A, Carbone DP** *et al.* (2015) Non-small-cell lung cancer. *Nature Rev*, **1**, 1–16.
2. **Travis WD, Brambilla E, Riely GJ** (2013) New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. *J Clin Oncol*, **31**, 992–1001.
3. **Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT** (2017) The Eighth Edition Lung Cancer Stage Classification. *Chest*, **151**, 193–203.
4. **National Cancer Institute.** *NCI Dictionary of Cancer Terms*. https://www.cancer.gov/publications/dictionaries/cancer-terms
5. **Kalemkerian GP, Narula N, Kennedy EB** *et al.* (2018) Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline update. *J Clin Oncol*, **36**, 911–19.
6. **Hanna N, Johnson D, Temin S** *et al.* (2017) Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline update. *J Clin Oncol*, **35**, 3484–515.
7. **Quint L** (2007) Staging non-small cell lung cancer. *Cancer Imaging*, **7**, 148–59.
8. **Neugut AI, Prigerson HG** (2017) Curative, life-extending, and palliative chemotherapy: new outcomes need new names. *Oncologist*, **22**, 883–5.
9. **Cooper SL, Brown PA** (2015) Treatment of pediatric acute lymphoblastic leukemia. *Ped Clin N Amer*, **62**, 61–73.
10. **Solomon BJ, Mok T, Kim D-W** *et al.* (2014) First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*, **371**, 2167–77.
11. **Hirsch FR, Scagliotti GV, Mulshine JL** *et al.* (2017) Lung cancer: current therapies and new targeted treatments. *Lancet*, **389**, 299–311. http://dx.doi.org/10.1016/S0140-6736(16)30958-8
12. **Kubiczkova L, Pour L, Sedlarikova L, Hajek R, Sevcikova S** (2014) Proteasome inhibitors—molecular basis and current perspectives in multiple myeloma. *J Cell Mol Med*, **18**, 947–61.
13. **BC Cancer**. *Cancer Drug Manual*. http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index#c-content
14. DeVita VT, Lawrence TS, Rosenberg SA (eds.) (2018) *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*, 11th edn, p. 2520. Wolters Kluwer, New York, NY.
15. **Reckamp K** (2016) *Lung Cancer: Treatment and Research*. Springer, Cham.
16. **Pujol J-L, Barlesi F, Daurès J-P** (2006) Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A meta-analysis of phase III randomized trials. *Lung Cancer*, **51**, 335–45.

17. **Markman M** (2003) Toxicities of the platinum antineoplastic agents. *Expert Opin Drug Saf*, **2**, 597–607.
18. **Hesketh PJ, Kris MG, Basch E** *et al.* (2017) Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline update. *J Clin Oncol*, **35**, 3240–61. doi: https://doi.org/10.1200/JCO.2017.74.4789
19. **Hartmann JT, Lipp H-P** (2003) Toxicity of platinum compounds. *Expert Opin Pharmacother*, **4**, 889–901.
20. **Azzoli CG, Baker Jr S, Temin S** *et al.* (2009) American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for Stage IV non-small-cell lung cancer. *J Clin Oncol*, **27**, 6251–66. doi: 10.1200/JCO.2009.23.5622
21. **Esfahani K, Meti N, Miller WH, Hudson M** (2019) Adverse events associated with immune checkpoint inhibitor treatment for cancer. *Can Med Assn J*, **191**, E40–6. doi: 10.1503/cmaj.180870
22. **Hellmann MD, Ciuleanu T-E, Pluzanski A** *et al.* (2018) Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*, **378**, 2093–104. doi: 10.1056/NEJMoa1801946
23. **Brahmer JR, Lacchetti C, Schneider BJ** *et al.* (2018) Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*, **36**, 1714–68. https://doi.org/10.1200/JCO.2017.77.6385
24. **Garant A, Guilbault C, Ekmekjian T** *et al.* (2017) Concomitant use of corticosteroids and immune checkpoint inhibitors in patients with hematologic or solid neoplasms: a systematic review. *Crit Rev Oncol Hematol*, **120**, 86–92. http://dx.doi.org/10.1016/j.critrevonc.2017.10.009
25. **Ricciuti B, Dahlberg SE, Adeni A** *et al.* (2019) Immune checkpoint inhibitor outcomes for patients with non-small-cell lung cancer receiving baseline corticosteroids for palliative versus non-palliative indications. *J Clin Oncol*, **37**, 1927–34. https://doi.org/10.1200/JCO.19.00189
26. **Maher VE, Fernandes LL, Weinstock C** *et al.* (2019) Analysis of the association between adverse events and outcome in patients receiving a programmed death protein 1 or programmed death ligand 1 antibody *J Clin Oncol*, **37**, 2730–7. https://doi.org/10.1200/JCO.19.00318
27. **Sato R, Samba R, Saya H, Arima Y** (2016) Concise review: stem cells and epithelial-mesenchymal transition in cancer: biological implications and therapeutic targets. *Stem Cells*, **34**, 1997–2007.
28. **de Martel C**, **Plummer M**, **Vignat J**, **Franceschi S** (2017) Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer*, **141**, 664–70.
29. **Melief CJM, van Hall T, Arens R, Ossendorp F, van der Burg SH** (2015) Therapeutic cancer vaccines, *J Clin Invest*, **125**, 3401–12. doi:10.1172/JCI80009
30. **Miliotou AN, Papadopoulou LC** (2018) CAR T-cell therapy: a new era in cancer immunotherapy. *Curr Pharma Biotech*, **19**, 5–18. doi: 10.2174/1389201019666180418095526
31. **June CH, Sadelain M** (2018) Chimeric antigen receptor therapy. *N Engl J Med*, **379**, 64–73. doi: 10.1056/NEJMra1706169
32. **Schuster SJ, Bishop MR, Tam CS** *et al.* (2019) Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*, **380**, 45–56. doi: 10.1056/NEJMoa1804980
33. **Nair C, Panikkar S, Ray A** (2014) How not to miss metastatic spinal cord compression. *Brit J Gen Pract*, **64**, e596–8. doi: 10.3399/bjgp14X681589
34. **da Silva GT**, **Bergmann A**, **Santos Thuler LC** (2017) Impact of symptomatic metastatic spinal cord compression on survival of patients with non-small-cell lung cancer. *World Neurosurg*, **108**, 698–704. https://doi.org/10.1016/j.wneu.2017.09.079
35. **Savage P, Sharkey R, Kua T** *et al.* (2014) Malignant spinal cord compression: NICE guidance, improvements and challenges. *Q J Med*, **107**, 277–82.

Chapter 23

Palliative care in heart failure

Michael Slawnych

'I wished I had my beta-blockers handy.'

James Whyte Black, Nobel Laureate, 1988

(Comment made when informed that he had won a Nobel prize for work leading to the development of propranolol)

Attitude

To enable each learner to:

- Recognize the uncertainty associated with prognostication in patients with heart failure.
- Reflect on the impact of polypharmacy on patients with heart failure.
- Understand the symptoms associated with heart failure and the benefits that palliative care can provide.

Skills

To enable each learner to:

- To describe the New York Heart Association (NYHA) and American College of Cardiology (ACC)/American Heart Association (AHA) heart failure classification schemes and how they relate to prognostication.
- To describe potential triggers for palliative care consultation in heart failure.
- To understand how to manage dyspnoea in patients with heart failure.

Knowledge

To enable each learner to:

- To understand the basic treatment of heart failure and how this impacts quality and quantity of life.
- To understand how to deactivate defibrillators.

Case 23.1

A.V. is a 71-year-old man with coronary artery disease. He had triple-vessel coronary artery bypass grafting carried out 20 years ago. He also underwent mechanical aortic valve replacement at the same time. Two years ago, he presented to hospital with an ST elevation myocardial infarction (MI). He underwent angioplasty at that time, with a stent placed in the left circumflex artery. Unfortunately, the hospitalization was complicated by cardiogenic shock and renal dysfunction, for which the patient required temporary inotrope support.

Michael Slawnych, *Palliative care in heart failure* In: *Palliative Medicine*. Edited by: Susan MacDonald, Leonie M. Herx, and Anne B. Boyle, Oxford University Press. © Oxford University Press 2022. DOI: 10.1093/oso/9780198837008.003.0023

A transthoracic echocardiogram was carried out several days after the patient was weaned from inotrope therapy and documented severe left ventricular systolic dysfunction, with an ejection fraction estimated at 20%. The anterior wall of the left ventricle was thinned and akinetic, consistent with a prior myocardial infarction. The patient remained in hospital for 2 weeks to improve volume status and renal function and also to advance medical therapy. His glomerular filtration rate (GFR) at the time of discharge was 30 ml/minute. Arrangements were made for ongoing follow-up in the heart function clinic.

Post-hospital discharge, the patient was able to walk a few blocks without experiencing significant dyspnoea. A repeat echocardiogram was carried out 3 months post-discharge and continued to document severe left ventricular systolic dysfunction. An electrocardiogram documented a left bundle branch block (LBBB) with a QRS duration of 160 ms. The patient was fully optimized with respect to medical therapy, which included a beta-blocker (carvedilol), the combination neprilysin inhibitor/angiotensin receptor blocker (sacubitril/valsartan), and a potassium-sparing diuretic (spironolactone). The patient was reviewed by a cardiac electrophysiologist who recommended implantation of a cardiac resynchronization therapy (CRT)–implantable cardioverter–defibrillator (ICD). This was implanted 2 weeks later.

Six months post-implantation of the CRT-ICD, the patient began to experience dyspnoea at progressively lower thresholds of activity, which then further progressed to dyspnoea at rest. The patient's weight was also increasing, and he gained 10 kg over a period of 14 days. The patient was reviewed by his cardiologist who diagnosed heart failure and thus intensified the patient's diuretic therapy. However, the patient's clinical status continued to decline, and he continued to experience significant dyspnoea at rest. At that point, he was hospitalized for worsening heart failure. Given his poor clinical status at that time, consideration was made for implantation of a ventricular assist device (VAD). Unfortunately, the patient was found not to be a suitable candidate.

Question 1. Why did the patient develop heart failure?

A.V. has significant coronary artery disease. He initially underwent surgical revascularization at age 51. He then went on to have an ST elevation MI 18 years later, with this hospitalization being complicated by cardiogenic shock. An echocardiogram carried out at that time documented an ejection fraction estimated at 20%, as well as evidence of a prior anterior MI. This is consistent with ischaemic cardiomyopathy, which is the most common cause of heart failure in the developed world.[1]

There are also several other causes of cardiomyopathy, including myocarditis, significant valvular heart disease, infiltrative diseases including amyloidosis and sarcoidosis, exposure to toxins such as alcohol (typically requires six or more drinks per day) and chemotherapeutic agents such as anthracyclines, autoimmune causes such as collagen vascular disease, tachycardia-induced (e.g. prolonged uncontrolled atrial fibrillation), and idiopathic (no clear aetiology identified).[2]

Question 2. How are classification systems, such as the NYHA class, useful in the assessment and management of symptoms of heart failure?

The NYHA classification scheme is commonly used to assess the severity of heart failure (see Figure 23.1a). This scheme categorizes patients on the basis of limitation of physical activity. The NYHA class is not static, with patients transitioning to lower classes (usually secondary to successful medical therapy) or higher classes (with clinical decline).

A.V. had symptoms at rest before hospitalization, giving him an NYHA classification of IV. The NYHA class is a predictor of survival in the ambulatory heart failure population, with patients in NYHA class IV having a 5-year mortality of the order of 60%.[3] With medical and device (e.g. CRT-ICD) therapy, many patients will improve and they will transition to lower NYHA classes. Conversely, patients can develop clinical worsening and transition to higher NYHA classes.

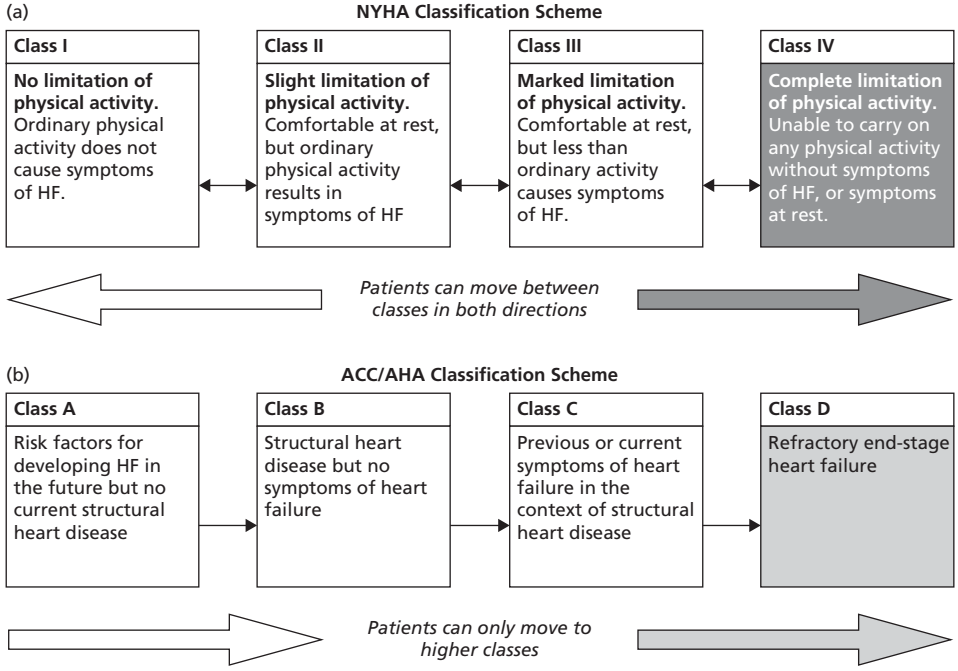


Fig. 23.1 NYHA and ACC/AHA heart failure classification schemes.

The NYHA classification system was first developed in 1928 and has undergone several revisions, most recently in 1994.[4] Of note, the 1964 Criteria Committee of the NYHA recognized that this scheme was 'only approximate' and also a subjective expression of physician opinion. Regardless, its ease of application has resulted in widespread use in many heart failure trials and international guidelines.[4,5]

The ACC, in conjunction with the AHA, developed a complementary four-category classification scheme (see Figure 23.1b). Unlike the NYHA scheme, patients in the ACC/AHA scheme can only move forward through the stages (e.g. once symptoms develop, stage C heart failure is present and a patient can never be re-classified as stage B). One of the goals of the ACC/AHA system is to identify patients at risk of developing heart disease and implementing medical therapy before symptoms develop, and therefore reducing morbidity and mortality.

The NYHA and ACC/AHA classification schemes are not directly interchangeable, with the NYHA scheme primarily applying to the severity of symptoms in patients who are in AHA/ACC stage B through D heart failure.

Question 3. What other common symptoms of heart failure does A.V. have?

Cardiologists are well versed in assessing dyspnoea using the NYHA class. However, this classification does not accurately portray the overall quality of life of patients with heart failure.[6] Heart failure patients can have symptom burdens similar to, or higher than, that in patients with advanced cancer.[7] Many times, hospitalization provides minimal symptom relief.

In A.V.'s case, he experienced not only significant dyspnoea, but also nausea, fatigue, and impaired mood. The typical symptoms experienced by patients with heart failure are summarized in Table 23.1.

Table 23.1 Common ambulatory heart failure symptoms and associated management

	Symptom	Pharmacological	Non-pharmacological
Traditional HF symptoms	Dyspnoea	◆ Optimized HF therapy (as per CCS guidelines) ◆ Inotropic agents (if consistent with goals of care) ◆ Consider subcutaneous furosemide ◆ Consider psychotropic: - First line: low-dose opioids - Second-line: benzodiazepines	◆ Rehabilitation/physical activity ◆ Energy conservation ◆ Positioning ◆ Supplemental oxygen if hypoxic ◆ Fan to circulate air
	Fatigue	◆ Optimized HF therapy (as per CCS guidelines)	◆ Rehabilitation/physical activity ◆ Consider depression, sleep disordered breathing, or other comorbidities
	Oedema	◆ Optimized HF therapy (as per CCS guidelines)	◆ Attention to skin care
Gastrointestinal symptoms	Nausea	◆ Optimized HF therapy (as per CCS guidelines) ◆ Promotility agents (metoclopramide) ◆ Haloperidol ◆ Ondansetron	◆ Small frequent meals
	Constipation	◆ Stimulant laxative (sennosides)	◆ Relax fluid restriction
	Abdominal fullness/ distension	◆ Intensify diuresis if ascites present	
Central nervous system symptoms	Depression	◆ Optimized HF therapy (as per CCS guidelines) ◆ Selective serotonin reuptake inhibitors (sertraline, citalopram) ◆ Avoid tricyclic antidepressants	◆ Psychotherapy ◆ Cognitive behaviour therapy ◆ Rehabilitation/physical activity
	Anxiety	◆ Consider and treat concomitant depression	◆ Supportive/psychotherapy ◆ Breathing exercises ◆ Relaxation therapy ◆ If related to ICD discharge, consider psychiatry review and adjusting settings or deactivation
	Sleep disturbance	◆ Optimized HF therapy (as per CCS guidelines) ◆ Consider and treat concomitant depression, anxiety, agitated delirium, nocturia, and sleep apnoea	◆ Attention to sleep hygiene
Other	Pain	◆ As per World Health Organization ladder (avoid non-steroidal anti-inflammatory drugs) ◆ Opioids	◆ Physical therapy ◆ Occupational therapy ◆ Massage

CCS, Canadian Cardiovascular Society; HF, heart failure.

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Question 4. What is the optimal medication treatment for patients with heart failure and severe left ventricular dysfunction?

Pharmacotherapy is an important component in the treatment of heart failure patients, and adherence to medications reduces mortality and helps to prevent hospitalization.[8,9]

Many decades ago, heart failure patients were treated with bed rest, sodium restriction, and digitalis.[10] Since that time, the neuro-hormonal hypothesis for heart failure was formulated and with this came a number of new therapies, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists.[8,11]

More recently, a medication combining an angiotensin receptor blocker (valsartan) with a neprilysin inhibitor (sacubitril) has been developed and shown to be superior to angiotensin-converting enzyme inhibitors in reducing the risk of heart failure death and of hospitalization.[12]

Heart failure exacerbations are typically managed with loop diuretics. Long-acting nitrates can also provide symptom relief.

Question 5. How many medications does the average heart failure patient take?

Current heart failure patients are older than in the past and commonly have several non-cardiovascular comorbidities.[13,14] As a result, they take a large number of medications.[15] A recent analysis of home care clients in Ontario showed that the majority of heart failure patients are taking nine or more medications.[16] As the number of elderly individuals is projected to increase for decades to come, the number of medications will likely increase correspondingly.[17]

Question 6. Why did the patient receive a CRT-ICD?

A.V. has severe left ventricular dysfunction. Despite being on optimal medical therapy, his cardiac function did not improve on repeat echocardiography carried out 3 months after the initial hospital discharge. As a result, he is at risk of life-threatening ventricular arrhythmias. Studies have shown that ICDs are effective in reducing this risk, for both primary prevention (patients who have not experienced any life-threatening ventricular arrhythmias to date) and secondary prevention (patients who have previously experienced life-threatening ventricular arrhythmias).[18,19]

The patient also has an LBBB pattern on electrocardiogram (ECG). The clinical status of some of these patients may improve in response to CRT pacing, in which pacemaker leads are placed in both the right and left ventricles, with both ventricles then being paced in unison or near unison. While most heart failure patients do not have a classic indication for a pacemaker in the strict sense of bradycardia support, several studies have shown that cardiac function may improve with CRT pacing.[20]

The Canadian Cardiovascular Society guidelines recommend CRT pacing for patients in sinus rhythm with: (1) NYHA class II, NYHA class III, or ambulatory NYHA class IV heart failure symptoms; (2) an ejection fraction of ≤35%; and (3) LBBB with a QRS duration of ≥130 ms. The guidelines go on to state that CRT pacing can be considered for patients in permanent atrial fibrillation who are otherwise candidates for this therapy.

Most patients who qualify for CRT pacing also meet the criteria for an ICD; however, a small subset of patients may opt for only CRT pacing, not wanting to be treated for life-threatening ventricular arrhythmias.

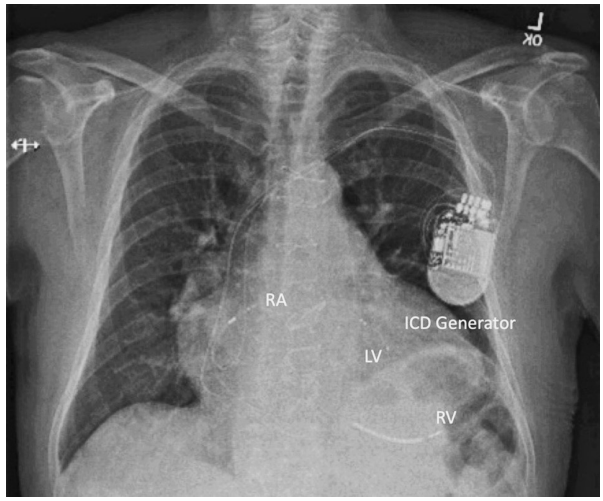


Fig. 23.2 The CRT-ICD system implanted in our patient. Posterior–anterior chest X-ray carried out post-implantation of CRT-ICD. Three leads can be observed on this chest X-ray, including a lead terminating in the right atrium (RA), a lead terminating in the right ventricle (RV), and a lead terminating in the left ventricle (LV). The RV lead is noted to be a defibrillator lead, as opposed to the other leads which are pacemaker leads. A defibrillator lead can be identified on the basis of thickening that is observed for the distal part of the lead—this represents the coil that is used to enact the defibrillation.

Question 7. What is the A.V.'s prognosis?

Approximately 5.7 million adults in the United States have heart failure.[21] Despite significant advances in medication and device therapy, prognosis remains poor for many patients. Depending on severity, heart failure patients face a broad range of annual mortality, ranging from 5% to 75%, with an overall average annual mortality of 24.3%.[22,23,24] However, patients have poor insight in this regard.[25,26,27] Even though heart failure causes more deaths than breast cancer, lung cancer, and prostate cancer combined, many patients are under the perception that heart failure is a benign condition in comparison to cancer.[28,29] This is not helped by the fact that physicians do not commonly discuss prognosis with heart failure patients, unless directly asked about it.[27] Fortunately, attitudes are changing, and many physicians are now advocating for discussing prognosis with heart failure patients.[30,31,32]

Prognostication in heart failure has proven to be quite challenging.[33] While the NYHA classification scheme is a common starting point for prognostication, over 100 variables have been linked to prognosis in heart failure and over 60 multi-variable prognostication models have been proposed in the literature.[30,34] The Seattle Heart Failure model is one of the more commonly employed models, and it provides estimates of 1-, 2-, and 3-year survival with the use of readily obtained clinical, pharmacological, laboratory, and device characteristics.[35] However, while many of these models perform fairly well at a population level, they do not do well at identifying which particular patients may be in their last months or year of life.[36,37] Perhaps more importantly, these models do not really identify heart failure patients that would benefit the most from the integration of palliative care.[38]

Unfortunately, the surprise question (e.g. 'Would I be surprised if this patient died in the next 12 months?') does not work well in non-cancer patient populations.[39] However, one of the

variables that has been consistently associated with poor prognosis is the number of heart failure hospitalizations, which can be further refined by age (see Figure 23.3).[40,41]

Many heart failure guidelines now incorporate prognosis as part of the recommended assessment for heart failure patients.[8,42,43] Moreover, validated heart failure risk models are endorsed by the ACC/AHA guidelines.[42,44] However, these same guidelines recognize the inherent difficulty of this process.

On the basis of two hospitalizations for heart failure in relatively short order, A.V.'s prognosis is poor, with a median life expectancy of 1.5 years.[40]

Case 23.1 (continued)

During the hospitalization, A.V. was reviewed by the palliative consult team. A low-dose opioid was recommended for the management of his dyspnoea; however, the patient declined it. In addition, the role of the patient's CRT-ICD was discussed and A.V. stated that he wished to keep his tachyarrhythmia therapies active.

The patient was discharged home 1 week later, with ongoing follow-up with the heart function clinic.

Question 8. When should palliative care be considered for patients with heart failure?

As highlighted in Question 7, prognostication challenges will not be overcome anytime soon. The initiation of palliative care should therefore be governed by symptom burden, and the major cardiovascular societies have adopted a needs-based approach in their guideline documents.[8,42,43]

Palliative care services are not widely extended to patients with heart failure. Even in countries with well-developed palliative consultation services, only around 4% of heart failure patients are referred for palliative care.[45] There is emerging evidence showing the benefit of palliative care for patients with heart failure.[46]

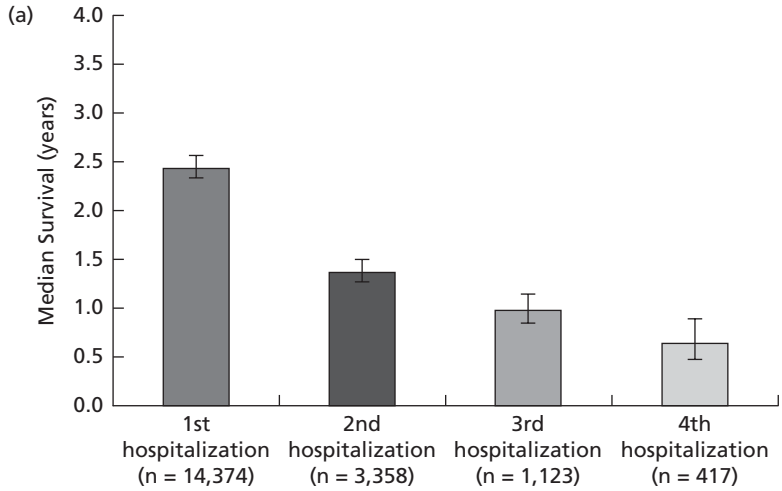
Box 23.1 shows some potential referral triggers that should be considered for the heart failure patient population.[69]

Question 9. What is the role for opioids in the relief of dyspnoea?

Dyspnoea is defined as an uncomfortable sensation of breathing.[47] The mechanism of dyspnoea has not been fully established. However, several contributing factors likely come into play, including respiratory effort, chemoreceptor stimulation, mechano-receptor stimulation, and neuro-ventilatory dissociation.[48] The actual experience of dyspnoea is influenced by interactions between physiological, psychological, social, and environmental factors.[49]

Dyspnoea is quite common in advanced heart failure, with many of these patients reporting this symptom to be 'very distressing', particularly near the end of life.[50] Opioids have been shown to reduce dyspnoea in a variety of diseases, including cancer, chronic obstructive pulmonary disease, and heart failure.[51,52] It is felt that opioids reduce dyspnoea in a similar manner to pain relief, namely by modulating the perception of dyspnoea.[53]

When used for the relief of dyspnoea, opioids are typically dosed at a lower range than for pain (e.g. hydromorphone 0.5 mg po three times a day PRN for dyspnoea). With appropriate dosing, there is no significant effect to the ventilatory drive.[52] Opioids are generally employed in those situations in which dyspnoea persists despite optimal medical therapy.



Median survival (50% mortality) and 95% confidence limits in patients with HF after each HF hospitalization.

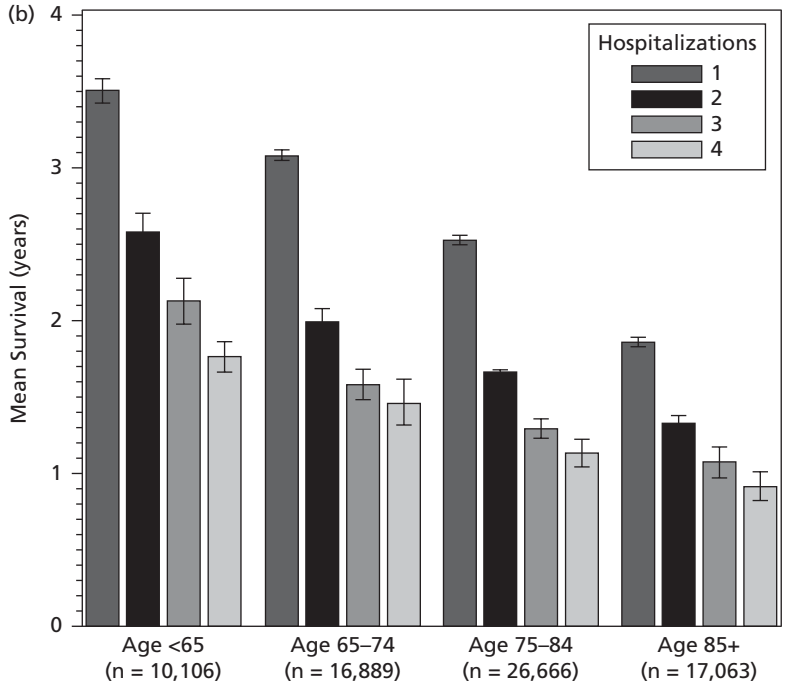


Fig. 23.3 (a) Median survival as a function of the number of heart failure hospitalizations in a community heart failure population.

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(b) Mean survival as a function of the number of heart failure hospitalizations and age group.

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Box 23.1 Potential triggers for specialist palliative care consultation in heart failure

ANY ONE of the following:

- Two or more hospital admissions for heart failure in the prior 6 months
- Two or more emergency department visits for heart failure in the prior 6 months
- Substantial worsening of prognosis or progressing disease
- NYHA class III or IV symptoms
- Substantial worsening or difficulty in controlling other physical or psychological symptoms from heart failure

AND AT LEAST ONE of the following:

- Consideration for, or ineligible, or not interested in, advanced heart failure therapies (outpatient inotropic infusion, left ventricular assist device, cardiac transplantation)
- Consideration for high-risk procedures (cardiac surgery, thoracic surgery)
- Consideration for ICD
- Consideration for feeding tube placement, tracheostomy, or initiation of renal replacement therapy
- Comorbidity (chronic renal failure, diabetes, cancer, stroke, cancer, human immunodeficiency virus, pulmonary fibrosis, oxygen-dependent chronic obstructive pulmonary disease)
- Previous/current intensive care/cardiac intensive care unit admission or cardiopulmonary resuscitation within past year
- Negative response to the 'surprise' question: 'would you be surprised if the patient died within 1 year?'
- Significant worsening of a comorbidity (e.g. oxygen requirement)
- Disagreements, uncertainty, or ethical concerns concerning treatment decisions or resuscitation preferences
- Perceived emotional, spiritual, or relational distress to patient, family, or surrogate
- Functional or cognitive decline, loss of independence, complex care requirements

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In addition to opioids, other treatments such as behavioural therapy and employing a fan to move air across the face have been found to be helpful.[54] Patients with significant dyspnoea often inquire about oxygen supplementation. However, this only appears to have a role if a patient is hypoxic.[55]

Question 10. Should any other therapies be offered at this time?

As stated earlier, A.V. is experiencing a number of symptoms, in addition to dyspnoea, including nausea, fatigue, and impaired mood. Table 23.1 lists some common treatment options for these additional symptoms.[69]

It should be added that A.V.'s overall quality of life is quite poor and his illness has led to significant psychosocial distress. While it is readily recognized that cancer patients can develop psychosocial distress as a result of their illness and associated treatments, this is less well known in non-cancer patient populations such as heart failure. Irrespective of the disease modality, palliative care interventions, in conjunction with psychological and psychiatric assistance, can help alleviate this psychosocial distress.

Question 11. Are patients with defibrillators receptive to having their shock therapies turned off in the setting of clinical deterioration?

Patients significantly overestimate the benefits of ICD tachyarrhythmia therapies (Figure 23.4a).[56] As a result, they are reluctant to have their tachyarrhythmia therapies deactivated, even when they are facing life-limiting non-cardiac illnesses such as terminal cancer (Figure 23.4b).[56]

Discussions about ICD tachyarrhythmia therapy deactivation should be the standard of care and should initially take place prior to implantation.[57,58] This should also be readdressed at annual heart failure reviews, after major milestones, and when the end of life appears to be approaching.[57]

The Canadian Cardiovascular Society/Canadian Heart Rhythm Society ICD Guidelines state that indications for considering ICD therapy discontinuation are life-threatening comorbidities, patient request, and situations in which an ICD is unlikely to increase life expectancy.[59]

Interestingly, patients who previously experienced a shock from their ICD were less likely to have their tachyarrhythmia therapies deactivated at the end of life than those who never had a shock.[60]

Case 23.1 (continued)

A.V. did well for approximately 6 weeks. He then began to again experience progressive dyspnoea and weight gain, which resulted in another hospitalization. Investigations carried at the beginning of this hospitalization revealed that his renal function had significantly deteriorated, with his GFR estimated to be 15 ml/minute. With intensification of diuretic therapy, this improved to a GFR of 25 ml/minute.

The patient was once again reviewed by the palliative consult team, and this time, he agreed to the introduction of low-dose hydromorphone for dyspnoea relief. A.V. also agreed to the discontinuation of his CRT-ICD tachyarrhythmia therapies.

After 2 weeks, A.V. was discharged home and was transitioned from the heart failure clinic to the heart failure home care team. However, his condition began to deteriorate shortly after discharge, and he was again hospitalized 5 days later. His renal function had further deteriorated, with a GFR of 10 ml/minute. The palliative care team again reviewed the patient and a decision was made to transition to comfort-focused care. The role of hospice was discussed; however, A.V. requested a preference to go home. His medication regimen was significantly simplified, keeping the beta-blocker, furosemide, and nitroglycerin patch (with the latter two medications being employed for symptom relief). A.V. was again discharged home with the support of the palliative home care team. He died 2 weeks later.

Question 12. Are there any guidelines for discontinuing medications used in the management of heart failure patients near the end of life?

The initiation of various therapies for heart failure patients is governed by widely available national/international guideline documents.[8,42,43] Conversely, there are no guidelines for the

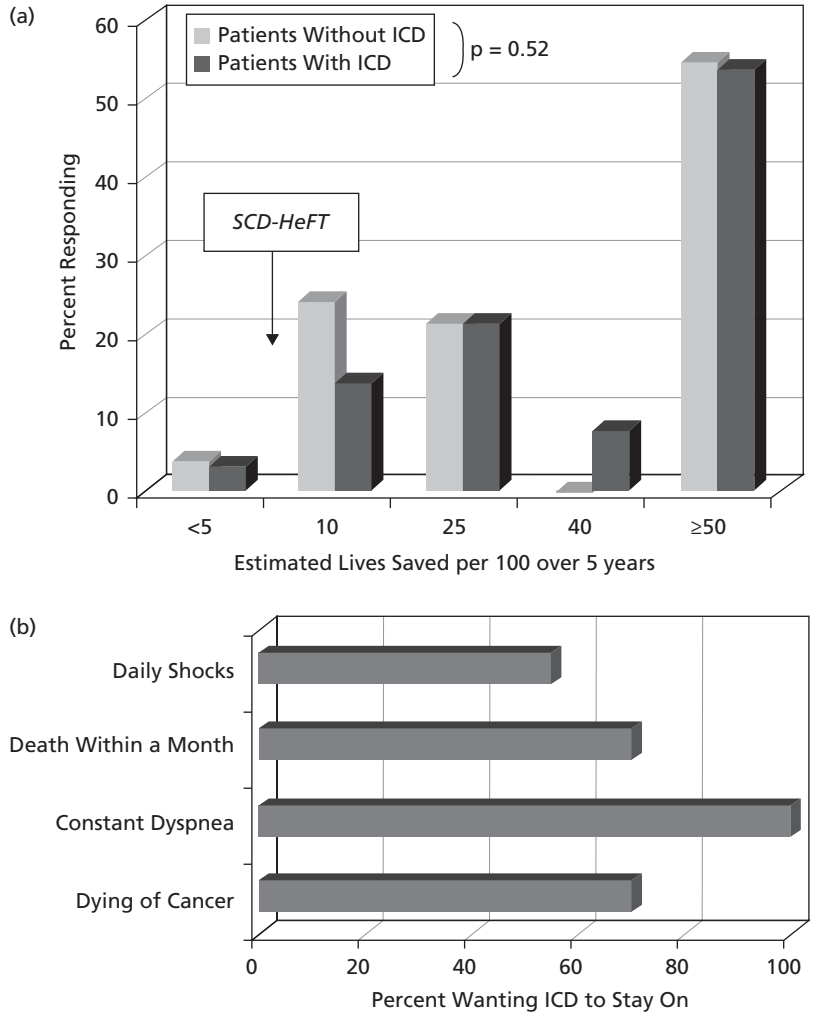


Fig. 23.4 (a) Subject estimates of how many lives per 100 they would expect an ICD to save during the first 5 years after implantation. Estimates were similar between ICD recipients and those without an ICD in place. The actual number of lives saved per 100 is 7.2, as per the Sudden Cardiac Death in Heart Failure Trial. (b) Responses of ICD recipients in terms of circumstances that might prompt ICD deactivation, showing that ICD recipients are reluctant to turn off defibrillator tachyarrhythmia therapies.

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discontinuation of heart failure therapies.[13] Practical constraints, such as hypotension and renal dysfunction, commonly dictate which medications are no longer continued. However, many times, there is no concerted effort to rationalize the medications that a patient is taking, and there are data to suggest that the number of medications in a general patient population increases as these patients near the end of life.[61]

Question 13. What is the likelihood of a patient receiving a shock from their defibrillator near the end of life?

More than 140 000 ICDs are implanted annually in the United States for primary prevention indications.[62]

Patients with heart failure are more likely to receive shocks as their conditions decline. Twenty per cent of patients with ICDs will receive a shock in the last few weeks of their life, with 8% receiving a shock within minutes of their deaths.[63] Discontinuation of ICD tachyarrhythmia therapies is an option available to all patients and can be carried out non-invasively by simply reprogramming the device. In the event that there is a delay to reprogramming, tachyarrhythmia therapies can be disabled by applying (and leaving) a magnet on the skin over the location of the ICD generator.

It is discouraging to note that patients are going to hospice with active ICDs. A 2010 survey showed that only 10% of American hospices had a policy addressing ICD deactivation. Nearly 60% of the surveyed hospices reported that at least one of their patients received a shock in the preceding year.[64]

Question 14. Where do patients with heart failure die?

In 2015, cardiovascular disease accounted for 32% of deaths in the United States, but only 16% of hospice deaths. The vast majority of heart failure deaths occur in hospital.[65,66] This is in contrast to public surveys showing that most people would prefer to die at home, provided that their care needs can be met and minimal burden is placed on their families.[38]

Interestingly, there are recent data that show cardiac patients who chose hospice lived longer than those who did not, challenging the notion that transition to hospice is inevitably associated with a shortened lifespan.[67,68]

References

1. **Briceno N**, **Schuster A**, **Lumley M**, **Perera D** (2016) Ischaemic cardiomyopathy: pathophysiology, assessment and the role of revascularisation. *Heart*, **102**(5), 397–406.
2. **Wu AH** (2007) Management of patients with non-ischaemic cardiomyopathy. *Heart*, **93**(3), 403–8.
3. **Arnold JMO**, **Liu P**, **Howlett J** *et al.* (2013) Ten year survival by NYHA functional class in heart failure outpatients referred to specialized multidisciplinary heart failure clinics 1999 to 2011. *Eur Heart J*, **34**(suppl_1), P1505.
4. **Raphael C**, **Briscoe C**, **Davies J** *et al.* (2007) Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. *Heart*, **93**(4), 476–82.
5. **Yap J**, **Lim FY**, **Gao F**, **Teo LL**, **Lam CS**, **Yeo KK** (2015) Correlation of the New York Heart Association classification and the 6-minute walk distance: a systematic review. *Clin Cardiol*, **38**(10), 621–8.
6. **Ward C** (2002) The need for palliative care in the management of heart failure. *Heart*, **87**(3), 294–8.
7. **Bekelman DB**, **Rumsfeld JS**, **Havranek EP** *et al.* (2009) Symptom burden, depression, and spiritual well-being: a comparison of heart failure and advanced cancer patients. *J Gen Intern Med*, **24**(5), 592–8.
8. **Ezekowitz JA**, **O'Meara E**, **McDonald MA** *et al.* (2017) 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the management of heart failure. *Can J Cardiol*, **33**(11), 1342–433.
9. **Fitzgerald AA**, **Powers JD**, **Ho PM** *et al.* (2011) Impact of medication nonadherence on hospitalizations and mortality in heart failure. *J Card Fail*, **17**(8), 664–9.
10. **Bruenn HG** (1970) Clinical notes on the illness and death of President Franklin D. Roosevelt. *Ann Intern Med*, **72**(4), 579–91.

11. **Packer M** (1992) The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol*, **20**(1), 248–54.
12. **McMurray JJ**, **Packer M**, **Desai AS** *et al.* (2014) Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*, **371**(11), 993–1004.
13. **Slawnych M**, **Simon J**, **Howlett J** (2012) The changing landscape—palliative care in the heart failure patient population. In: Chang E (ed.) *Contemporary and Innovative Practice in Palliative Care*. InTech.
14. **Jones NR**, **Hobbs FDR**, **Taylor CJ** (2017) The management of diagnosed heart failure in older people in primary care. *Maturitas*, **106**, 26–30.
15. **Wong CY**, **Chaudhry SI**, **Desai MM**, **Krumholz HM** (2011) Trends in comorbidity, disability, and polypharmacy in heart failure. *Am J Med*, **124**(2), 136–43.
16. **Foebel AD**, **Hirdes JP**, **Heckman GA**, **Tyas SL**, **Tjam EY** (2011) A profile of older community-dwelling home care clients with heart failure in Ontario. *Chronic Dis Can*, **31**(2), 49–57.
17. **Foot DK**, **Lewis RP**, **Pearson TA**, **Beller GA** (2000) Demographics and cardiology, 1950–2050. *J Am Coll Cardiol*, **35**(5 Suppl B), 66B–80B.
18. **Moss AJ**, **Zareba W**, **Hall WJ** *et al.* (2002) Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*, **346**(12), 877–83.
19. **Bardy GH**, **Lee KL**, **Mark DB** *et al.* (2005) Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*, **352**(3), 225–37.
20. **Exner DV**, **Birnie DH**, **Moe G** *et al.* (2013) Canadian Cardiovascular Society guidelines on the use of cardiac resynchronization therapy: evidence and patient selection. *Can J Cardiol*, **29**(2), 182–95.
21. **Mozaffarian D**, **Benjamin EJ**, **Go AS** *et al.* (2016) Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*, **133**(4), e38–360.
22. **Aaronson KD**, **Schwartz JS**, **Chen TM**, **Wong KL**, **Goin JE**, **Mancini DM** (1997) Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation*, **95**(12), 2660–7.
23. **Rose EA**, **Moskowitz AJ**, **Packer M** *et al.* (1999) The REMATCH trial: rationale, design, and end points. Randomized evaluation of mechanical assistance for the treatment of congestive heart failure. *Ann Thorac Surg*, **67**(3), 723–30.
24. **O'Meara E**, **Thibodeau-Jarry N**, **Ducharme A**, **Rouleau JL** (2014) The epidemic of heart failure: a lucid approach to stemming the rising tide. *Can J Cardiol*, **30**(12 Suppl), S442–54.
25. **Willems DL**, **Hak A**, **Visser F**, **Van der Wal G** (2004) Thoughts of patients with advanced heart failure on dying. *Palliat Med*, **18**(6), 564–72.
26. **Wotton K**, **Borbasi S**, **Redden M** (2005) When all else has failed: nurses' perception of factors influencing palliative care for patients with end-stage heart failure. *J Cardiovasc Nurs*, **20**(1), 18–25.
27. **Allen LA**, **Yager JE**, **Funk MJ** *et al.* (2008) Discordance between patient-predicted and model-predicted life expectancy among ambulatory patients with heart failure. *JAMA*, **299**(21), 2533–42.
28. **Selman L**, **Harding R**, **Beynon T** *et al.* (2007) Improving end-of-life care for patients with chronic heart failure: 'Let's hope it'll get better, when I know in my heart of hearts it won't'. *Heart*, **93**(8), 963–7.
29. **Adler ED**, **Goldfinger JZ**, **Kalman J**, **Park ME**, **Meier DE** (2009) Palliative care in the treatment of advanced heart failure. *Circulation*, **120**(25), 2597–606.
30. **Allen LA**, **Stevenson LW**, **Grady KL** *et al.* (2012) Decision making in advanced heart failure: a scientific statement from the American Heart Association. *Circulation*, **125**(15), 1928–52.
31. **Weis M** (2017) Critical points for the practising cardiologist to consider in their patients with end-stage heart failure. *E-Journal of Cardiology Practice*, **14**(42).
32. **Simpson J**, **McMurray JJV** (2018) Prognostic modeling in heart failure: time for a reboot. *JACC Heart Fail*, **6**(6), 463–4.
33. **Aaronson KD**, **Cowger J** (2012) Heart failure prognostic models: why bother? *Circ Heart Fail*, **5**(1), 6–9.

34. **Pham H**, **Nguyen Q**, **Pham N**, **Dinh L**, **Le N** (2019) Evaluation of prognosis models in patients with heart failure. *J Am Coll Cardiol*, **73**(9, Supplement 1), 888.
35. **Levy WC**, **Mozaffarian D**, **Linker DT** *et al.* (2006) The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*, **113**(11), 1424–33.
36. **Allen LA**, **Matlock DD**, **Shetterly SM** *et al.* (2017) Use of risk models to predict death in the next year among individual ambulatory patients with heart failure. *JAMA Cardiol*, **2**(4), 435–41.
37. **Haga K**, **Murray S**, **Reid J** *et al.* (2012) Identifying community based chronic heart failure patients in the last year of life: a comparison of the Gold Standards Framework Prognostic Indicator Guide and the Seattle Heart Failure Model. *Heart*, **98**(7), 579–83.
38. **Hogg KJ**, **Jenkins SM** (2012) Prognostication or identification of palliative needs in advanced heart failure: where should the focus lie? *Heart*, **98**(7), 523–4.
39. **Downar J**, **Goldman R**, **Pinto R**, **Englesakis M**, **Adhikari NK** (2017) The 'surprise question' for predicting death in seriously ill patients: a systematic review and meta-analysis. *CMAJ*, **189**(13), E484–93.
40. **Setoguchi S**, **Stevenson LW**, **Schneeweiss S** (2007) Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J*, **154**(2), 260–6.
41. **Lin AH**, **Chin JC**, **Sicignano NM**, **Evans AM** (2017) Repeat hospitalizations predict mortality in patients with heart failure. *Mil Med*, **182**(9), e1932–7.
42. **Yancy CW**, **Jessup M**, **Bozkurt B** *et al.* (2013) 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*, **62**(16), e147–239.
43. **Ponikowski P**, **Voors AA**, **Anker SD** *et al.* (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Rev Esp Cardiol (Engl Ed)*, **69**(12), 1167.
44. **Levy WC**, **Anand IS** (2014) Heart failure risk prediction models: what have we learned? *JACC Heart Fail*, **2**(5), 437–9.
45. **Riley JP**, **Beattie JM** (2017) Palliative care in heart failure: facts and numbers. *ESC Heart Fail*, **4**(2), 81–7.
46. **Rogers JG**, **Patel CB**, **Mentz RJ** *et al.* (2017) Palliative Care in Heart Failure: the PAL-HF randomized, controlled clinical trial. *J Am Coll Cardiol*, **70**(3), 331–41.
47. **Manning HL**, **Schwartzstein RM** (1995) Pathophysiology of dyspnea. *N Engl J Med*, **333**(23), 1547–53.
48. **Manning HL**, **Mahler DA** (2001) Pathophysiology of dyspnea. *Monaldi Arch Chest Dis*, **56**(4), 325–30.
49. [**No authors listed**] (1999) Dyspnea. Mechanisms, assessment, and management: a consensus statement. American Thoracic Society. *Am J Respir Crit Care Med*, **159**(1), 321–40.
50. **McCarthy M**, **Lay M**, **Addington-Hall J** (1996) Dying from heart disease. *J R Coll Physicians Lond*, **30**(4), 325–8.
51. **Jennings AL**, **Davies AN**, **Higgins JP**, **Gibbs JS**, **Broadley KE** (2002) A systematic review of the use of opioids in the management of dyspnoea. *Thorax*, **57**(11), 939–44.
52. **Hochgerner M**, **Fruhwald FM**, **Strohscheer I** (2009) Opioids for symptomatic therapy of dyspnoea in patients with advanced chronic heart failure—is there evidence? *Wien Med Wochenschr*, **159**(23–24), 577–82.
53. **Muers MF** (2002) Opioids for dyspnoea. *Thorax*, **57**(11), 922–3.
54. **Galbraith S**, **Fagan P**, **Perkins P**, **Lynch A**, **Booth S** (2010) Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. *J Pain Symptom Manage*, **39**(5), 831–8.
55. **Abernethy AP**, **McDonald CF**, **Frith PA** *et al.* (2010) Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet*, **376**(9743), 784–93.
56. **Stewart GC**, **Weintraub JR**, **Pratibhu PP** *et al.* (2010) Patient expectations from implantable defibrillators to prevent death in heart failure. *J Card Fail*, **16**(2), 106–13.

57. **Matlock DD**, **Stevenson LW** (2012) Life-saving devices reach the end of life with heart failure. *Prog Cardiovasc Dis*, **55**(3), 274–81.
58. **Lampert R**, **Hayes DL**, **Annas GJ** *et al.* (2010) HRS Expert Consensus Statement on the Management of Cardiovascular Implantable Electronic Devices (CIEDs) in patients nearing end of life or requesting withdrawal of therapy. *Heart Rhythm*, **7**(7), 1008–26.
59. **Bennett M**, **Parkash R**, **Nery P** *et al.* (2017) Canadian Cardiovascular Society/Canadian Heart Rhythm Society 2016 Implantable Cardioverter-Defibrillator Guidelines. *Can J Cardiol*, **33**(2), 174–88.
60. **Hill L**, **McIlfatrick S**, **Taylor BJ** *et al.* (2016) Implantable cardioverter defibrillator (ICD) deactivation discussions: reality versus recommendations. *Eur J Cardiovasc Nurs*, **15**(1), 20–9.
61. **Morin L**, **Vetrano DL**, **Rizzuto D**, **Calderón-Larrañaga A**, **Fastbom J**, **Johnell K** (2017) Choosing wisely? Measuring the burden of medications in older adults near the end of life: nationwide, longitudinal cohort study. *Am J Med*, **130**(8), 927–36.e929.
62. **Campbell RT**, **Jackson CE**, **Wright A** *et al.* (2015) Palliative care needs in patients hospitalized with heart failure (PCHF) study: rationale and design. *ESC Heart Fail*, **2**(1), 25–36.
63. **Goldstein NE**, **Lampert R**, **Bradley E**, **Lynn J**, **Krumholz HM** (2004) Management of implantable cardioverter defibrillators in end-of-life care. *Ann Intern Med*, **141**(11), 835–8.
64. **Goldstein N**, **Carlson M**, **Livote E**, **Kutner JS** (2010) Brief communication: management of implantable cardioverter-defibrillators in hospice: a nationwide survey. *Ann Intern Med*, **152**(5), 296–9.
65. **Khand AU**, **Gemmell I**, **Rankin AC**, **Cleland JG** (2001) Clinical events leading to the progression of heart failure: insights from a national database of hospital discharges. *Eur Heart J*, **22**(2), 153–64.
66. **Warraich HJ**, **Hernandez AF**, **Allen LA** (2017) How medicine has changed the end of life for patients with cardiovascular disease. *J Am Coll Cardiol*, **70**(10), 1276–89.
67. **Gelfman LP**, **Barrón Y**, **Moore S** *et al.* (2018) Predictors of hospice enrollment for patients with advanced heart failure and effects on health care use. *JACC Heart Fail*, **6**(9), 780–9.
68. **Warraich HJ**, **Rogers JG** (2018) It is time to discuss dying. *JACC Heart Fail*, **6**(9), 790–1.
69. **Slawnych M** (2018) New dimensions in palliative care cardiology. *Can J Cardiol*, **34**(7), 914–24.

Chapter 24

Neurological disorders

Teneille Gofton

Attitude

To enable each learner to:

- Reflect upon the importance of patient values and goals of care in clinical decision-making in neurological disorders.

Skills

To enable each learner to:

- Demonstrate an approach to eliciting patient values and goals of care and discussing prognosis in order to develop an appropriate treatment plan congruent with patient wishes.

Knowledge

To enable each learner to:

- Construct a treatment plan in keeping with the goals of care for a person with dysphagia as a result of neurological disorders.
- Recognize the consequences of abrupt dopaminergic medication withdrawal and anti-dopaminergic medications in people with Parkinson's disease.
- Develop a strategy for seizure management at the end of life.

Introduction

Palliative care in neurological disorders is challenging on many levels. Many neurodegenerative or inflammatory disorders progress with variable illness trajectories, for example Alzheimer's disease, frontotemporal dementia, or multiple sclerosis (MS), making prognostic discussions particularly difficult, while other diseases in the neurosciences present as an acute and catastrophic life-changing or life-threatening event (e.g. stroke, subarachnoid haemorrhage) in an individual with previously normal function. Palliative care in neurological disorders also includes oncological care, primarily for people with cerebral metastases, but also for people with primary brain tumours or paraneoplastic syndromes. In these instances, the timing for incorporation of a palliative approach to care may be more clear than in non-oncological cases.

Additional challenges specific to palliative care in neurological disorders include communication barriers, ranging from dysarthria to aphasia, and loss of personhood secondary to functional and cognitive changes that may occur very early in the illness trajectory. Furthermore, people with neurological disorders may live for prolonged periods of time with cumulative physical and

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Table 24.1 Three common illness trajectories in the palliative neurosciences

Category	Acute catastrophic brain injury	Acute or relapsing, with recovery	Neurodegenerative
Examples	Intracerebral haemorrhage, traumatic brain injury, subarachnoid haemorrhage	Ischaemic stroke, multiple sclerosis	Parkinson's disease, amyotrophic lateral sclerosis
Expected course	Imminently dying, impaired level of consciousness	Acute functional deterioration with potential for at least partial recovery, recurrence, and future progression	Cumulative disability with increasing risk of life-threatening complications

cognitive impairments, resulting in high care needs that can pose a significant burden on loved ones and caregivers.

Table 24.1 outlines three common illness trajectories in neurological disorders. Regardless of the illness trajectory, incorporation of a palliative approach to care begins at the time of diagnosis and immediately thereafter, such as when breaking bad news in the case of catastrophic neurologic injuries and when discussing prognosis with patients and their loved ones. Over the course of the illness trajectory, a palliative approach to care may be more or less required, depending on the patient's psychosocial and medical needs and while disease-specific management is ongoing. Advance care planning, including preferences regarding nutritional/hydration/respiratory supports, caregiver and family support, and location of death, is necessary in cases of progressive illness, and goals of care must be formally assessed and discussed. Bereavement care is also essential, especially in cases where there is progressive decline and an increased likelihood for anticipatory bereavement.

Despite these three common illness trajectories, there is considerable variation within each trajectory, making prognostication very challenging. However, there are indicators that can help to predict when a prognosis may be less than 5 months. In progressive diseases, such as amyotrophic lateral sclerosis (ALS), MS, or Parkinson's disease, an ongoing physical and/or cognitive deterioration (including progressive dysarthria or dysphagia, recurrent aspiration pneumonias, feeling breathless, or respiratory failure) despite best therapies can signal that the end of life may be near.[1] In dementia, a loss of ability to perform two or more activities of daily living within a 6-month period or dysphagia may signal that the end of life is near.[1] Table 24.2 outlines a systematic approach to issues that may arise for people with advanced neurological disorders. These issues will be explored in more detail throughout this chapter.

Cerebrovascular disease

Stroke is an acute-onset, potentially life-threatening disease that may occur due to death of cerebral tissue. Stroke is classified based on the cause and may occur due to ischaemia of the brain (ischaemic stroke), a haemorrhage into the brain parenchyma (intracerebral haemorrhage), or a haemorrhage into the cerebrospinal fluid, with or without direct brain tissue injury, as a result of a ruptured intracranial aneurysm (subarachnoid haemorrhage).[2] The most common cause of stroke is an acute ischaemic stroke which occurs due to occlusion of a cerebral blood vessel that leads to infarction of the downstream brain tissue.[2]

Case 24.1

C.D., a previously healthy 78-year-old widow, was found unconscious at home on the floor after an undetermined period of time. She is aphasic and hemiplegic on the right side. She is brought to the emergency

Table 24.2 The ABCs of neuropalliative care: common areas of concern in the neurosciences at the end of life

		Problem	Palliative care goals
A	Airway	Secretions and risk of aspiration	Symptom management; recognizing limits of feeding tube to minimize risks
B	Breathing	Respiratory failure (ALS) or pneumonia	Medical symptom management with or without mechanical ventilation
C	Comfort	Musculoskeletal and skin integrity	Reducing pain and discomfort related to immobility/role of non-pharmacological management
	Cognition	Cognitive impairment (overt, subtle, or none)	Identifying limited capacity for decision-making, impact on outcomes
	Communication	Motor (dysarthria) or language (aphasia) impairment	Developing communication strategies for symptom assessment, as well as for expressing personal goals
D	Decision-making	Preparing for sudden changes in status, documentation of overall goals of care	Decisions to accept or forgo interventions require clear planning for alternative symptom management
E	Expectations	Recognizing the limitations of medical interventions	Identifying the consequences of care decisions and their impact on expressed goals
F	Feeding	Nutritional support and medical delivery	Feeding tubes are recommended in specific circumstances, based on stage of disease and anticipated use, not on aspiration risk

ALS, amyotrophic lateral sclerosis.

department by ambulance and the stroke team concludes that based on her clinical and radiological findings, she is a candidate for aggressive medical therapy for a left middle cerebral artery occlusion. C.D. is given a nasogastric tube and intravenous thrombolytics and undergoes an endovascular procedure in an attempt to extract the clot causing the ischaemic stroke. Unfortunately, her therapy is not successful. After 24 hours, she has not improved at all and she remains aphasic, hemiplegic, hemianaesthetic, and unable to swallow. The expected long-term deficits associated with the area of infarction include right-sided hemiplegia and hemianaesthesia, as well as global aphasia. C.D. is becoming more somnolent and is having difficulty managing her secretions. She has developed a fever and is suspected of having an aspiration pneumonia.

Question 1. What are the common options for feeding after a stroke?

There are four possible options for nutrition after a stroke or other neurological event resulting in dysphagia, including oral intake, nasogastric tube feeding, percutaneous endoscopic gastrostomy (PEG) feeding, and no enteral feeding. The most appropriate choice requires the treating medical team to have a clear understanding of the patient's values and goals of care.

Oral intake may be continued in a comfort-focused manner and based on patient desires. However, any time there is dysphagia, then oral feeding carries a risk of aspiration and pneumonia. Feeding should be guided by the patient, based on their level of consciousness and whether or not they express an interest in oral intake. Small amounts of food can be offered by hand to the patient. The patient should be appropriately positioned upright and food consistency should be modified in order to minimize the risk of aspiration or of distressing coughing. If an aspiration pneumonia does occur, then it can be managed symptomatically, without antibiotics, by using medications to treat pain or dyspnoea. The treatment plan for an aspiration pneumonia should be established with the patient and/or substitute decision-maker prior to initiating oral feeding.

Nasogastric tube feeding is often used in the acute stages following a stroke or other catastrophic neurologic injury. This is to allow for the administration of orally administered medications despite the presence of dysphagia or impaired consciousness. The Canadian Best Practice Recommendations[3] suggest early nasogastric tube feeding to enable the best possible recovery after a stroke. However, using a nasogastric tube to support feeding does not reduce the risk of aspiration and early nasogastric tube feeding increases the risk of gastric bleeding.[4] The nasogastric tube is used as a time-limited trial for several reasons: (1) patients may regain the ability to swallow safely within a short period of time after a stroke; (2) patients may not regain the ability to swallow safely but have agreed to placement of a more permanent feeding tube; (3) patients may dislodge the nasogastric feeding tube regularly; and (4) patients and caregivers may decide that nutritional support is not in keeping with their ultimate values and goals for care. The time-limited nature of the nasogastric tube feeding trial should be made clear to families and caregivers from the outset.

PEG feeding is not recommended immediately following a stroke.[5] There is an increased risk of death and poor outcome, when compared to nasogastric tube feeding, in the acute period after a stroke. Gastrostomy can be considered in cases where continued nutritional support is meeting that patient's goals of care and if swallowing has not improved after a period of nasogastric tube feeding.

No oral or enteral feeding is an option in comfort-focused care for people with severely impaired swallowing and at the end of life. Typically, the person has an impaired level of consciousness and shows no clear interest in oral intake. Death is usually imminent and the patient is severely distressed after oral intake because of severe coughing or choking. As in any other case, the person should be provided with attentive mouth care to avoid dry mouth and associated discomfort.

Case 24.1 (continued)

You meet with C.D.'s sons. They have differing views on what the next step should be. They have never spoken with her regarding her wishes for healthcare in the event of a stroke and they are struggling to interpret her generic advance directive. One son thinks that his mother would not want her life to be prolonged, given that she will be both dependent for care and unable to communicate. The other son is worried that his mother will suffer if the feeding tube that is currently in place is removed and nutritional supports are not continued. He is concerned that she will 'starve to death'.

Question 2. How would you respond to the son's fears that his mother will 'starve to death'?

Families and caregivers are often worried about their loved one starving to death or becoming thirsty. Decisions concerning feeding and hydration are also an area for potential conflict within the healthcare team.[6] Providing food is a fundamental part of the way that people show they love

and care for someone. Food is also essential for survival. Therefore, it is important to validate the son's concerns about his mother starving to death.

A discussion about the ethical issues related to artificial nutrition and hydration is covered in other literature.[7,8]

Important elements of the discussion with C.D.'s sons that you should consider include:

- Listening to, and validating, the distress that C.D.'s sons are experiencing.
- Exploring the sons' understanding of their mother's values, healthcare status, prognosis, and wishes for healthcare, taking into consideration her recent stroke.
- Acknowledging that uncertainties remain with respect to C.D.'s ultimate clinical outcome and reviewing the foreseeable outcomes with each of the feeding options.
- Reviewing C.D.'s prognosis and her goals of care.
- Empathizing with C.D.'s sons and validating that they may feel conflicted between a wish for their mother to survive and a wish for her to have a comfortable death.

Question 3. How would you establish the goals of care for C.D.?

Establishing a clear understanding of a patient's values and wishes for healthcare is paramount to developing an appropriate treatment plan for the patient. C.D. is aphasic and is not able to participate in her own decision-making process. She has not previously discussed her wishes for healthcare with her family and so they are left wondering what to do in the current situation. You discuss C.D.'s case with the neurology team in order to fully understand her prognosis. Given the size of her stroke and the increasing somnolence, the neurology team is concerned that C.D. will die from the stroke. You sit down with her sons with the goal of determining what is important to C.D. in her daily life. This information will provide a context for future discussions regarding C.D.'s goals of care and her treatment plan.

Establishing the patient's values and goals of care is an important first step in developing an overall treatment plan and in initiating advance care planning. After determining the patient's personal values and wishes for healthcare at the end of life, the prognosis should be disclosed to the patient and/or their loved ones. The treatment options, associated risks and benefits, and expected clinical outcomes should be discussed openly. Finally, the overall treatment plan should be agreed upon. The discussions and decisions that take place should be documented in the medical record to enable consistency of care at the end of life or to inform future decisions that may need to be made.

Take-home points are:

- Patient values and goals of care need to be discussed in order to inform the development of a treatment plan aligned with their values and wishes.
- Communication impairment is common in neurological disorders and so we must frequently rely upon the patient's loved ones or substitute decision-makers to help inform treatment decisions.
- Decisions regarding nutritional support after an acute catastrophic brain injury need to be made on a case-by-case basis and should be aligned with the overall goals of care and treatment plan for each individual case.

Motor neuron disease

ALS is the most common motor neuron disease. It causes progressive weakness, dysarthria, dysphagia, neuromuscular respiratory failure, emotional lability, and cognitive impairment

with features similar to those seen in frontotemporal dementia. The vast majority of ALS occurs sporadically, but there are also uncommon familial forms. ALS usually presents between 55 and 75 years of age; however, it may present much earlier or later in life.[9] ALS is a progressive neurodegenerative illness without a cure. Medical interventions, such as nutritional and ventilatory supports, may improve survival and quality of life in ALS[9] and various degrees of medical supports may be incorporated into care as the disease progresses, based on patient values and goals of care.

People living with ALS have a high burden of symptoms that develop relatively rapidly over months (see Table 24.3).[10] Coordinating the care required for a person with ALS can be challenging, depending on the resources within the community. Evidence shows that multidisciplinary ALS clinics with nursing, physiotherapy, occupational therapy, speech language pathology, neurology, and palliative medicine specialists in one place are beneficial from the point of view of both survival and quality of life.[11]

Case 24.2

B.F. is a 65-year-old man who was diagnosed with ALS 6 months ago after he was referred to a neurologist for progressive, but mild, shortness of breath and right-hand weakness. Over the last 6 months, B.F. has experienced increasing shortness of breath and weakness of all four extremities. He remains ambulatory at home but now uses a wheelchair for longer trips outside of the home. He has developed dysarthria and he coughs intermittently with oral intake. He has lost 8 kg over the last 3 months. The palliative care team is asked to see B.F. today at the multidisciplinary ALS clinic where he has previously been seen twice. Today, the speech language pathologist assessed B.F. and recommended consistency modifications to his diet because he was noted to have dysphagia and an increased risk of aspiration.

Question 4. What is the role of nutritional support in ALS?

Progressive dysphagia is seen in the majority of people with ALS and can result in choking, aspiration pneumonia, and weight loss.[12] Assessment of swallowing by a speech language pathologist is indicated for anyone with ALS who has been coughing after oral intake of liquids or solids or who has increasing dysarthria. Earlier in the disease trajectory, modifications in food consistency, such as thickeners for liquids and minced or pureed solids, as well as the addition of nutritional supplements, may help alleviate symptoms and reduce weight loss. As the disease progresses and dysphagia worsens, medical support in the form of a radiologically inserted gastrostomy tube may be considered to provide nutritional support and to administer medications. Because the feeding tube itself does not prevent the risk of aspiration and because it is being used to supplement total daily calories in order to maintain body weight, a patient does not need to give up oral intake once a feeding tube is placed. The goal of the feeding tube is to reduce the degree of weight loss and to provide an alternate route for medication administration.[12] There are no studies to guide the optimal timing for insertion of a gastrostomy tube and so it should be considered on a case-by-case basis as dysphagia emerges. In addition to preventing weight loss, nutritional support via a gastrostomy tube is thought to prolong survival in people with ALS.[12]

Question 5. What is the role of ventilatory support in ALS?

The most common cause of death in ALS is progressive neuromuscular respiratory failure.[12] Patients are monitored for evidence of respiratory failure when they are seen at multidisciplinary

Table 24.3 Prevalent symptoms and their management in ALS

Symptom	Mechanism	Management: non-pharmacological	Management: pharmacological
Joint pain (hip, back, shoulders commonly)	Immobility, spasticity, arthritis	Physical therapy (active and passive range of motion)	Oral or topical non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections, analgesics
Cramps, muscle spasms	Immobility, spasticity	Physical therapy, massage, positioning, seating	Anti-spasticity agents (e.g. baclofen), muscle relaxants, benzodiazepines (e.g. clonazepam), gabapentin
Aching, non-specific muscular discomfort	Immobility, dependent oedema, nocturnal hypoventilation	Massage, positioning, elevation of limbs, compressive stockings, non-invasive ventilation	Tricyclic antidepressants (e.g. amitriptyline)
Neuropathic pain (burning, lancinating, paraesthesiae)	Nerve compression syndromes, spinal stenosis, radiculopathy	Positioning, splints where appropriate	Local anaesthesia or corticosteroid injections where appropriate, gabapentin or pregabalin, tricyclic antidepressants, analgesics
Headache	Nocturnal hypoventilation, positioning, tension, migraine	Non-invasive ventilation, massage, trigger identification and avoidance	Diagnosis-dependent
Secretions	Impaired swallowing, nasal congestion/post-nasal drip, respiratory failure	Oral hygiene, cleansing agents, non-invasive ventilation	Anticholinergic drugs (e.g. atropine, scopolamine, glycopyrrolate), amitriptyline, bronchodilators
Skin irritation	Immobility (pressure points), drooling (peri-oral)	Positioning, barrier ointments/creams	

Source: data from Miller RG, et al. 'Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology'. Neurology Vol 73, Issue 15, pp.1227–33, (2009) Wolters Kluwer11; and Meunier CL, et al. 'A new approach to homeostatic regulation: towards a unified view of physiological and ecological concepts'. PLoS One (2014), Vol. 9, Issue 9, pp.e107737. (2014) PLOS10

ALS clinics or assessed by a physician. In Canada, there is some regional variation (due to availability of resources) regarding which objective measurements are used to monitor respiratory function. Pulmonary function tests, including upright and supine forced vital capacity and maximal inspiratory pressure, overnight oximetry, or sniff nasal pressure may all be used to monitor respiratory function.[12]

Non-invasive ventilation is used for respiratory support in ALS and has been shown to have a survival benefit and to slow the rate of respiratory decline, as measured with forced vital capacity.[12] Studies have also shown that non-invasive ventilation has a positive impact on quality of life in ALS and reduces dyspnoea.[12] Earlier initiation of non-invasive ventilatory support has been associated with improved tolerance and compliance over time.[12] Some patients will elect to have tracheal invasive ventilation as their disease progresses. Tracheal

invasive ventilation may also have some positive effect on quality of life in people with ALS, but it creates a significantly higher care burden for caregivers and loved ones.[12] Prior to initiating any ventilatory support, discussions regarding its eventual discontinuation should be held so that patients and substitute decision-makers can make an informed choice regarding their future care. While uncommon, in cases in which a person with ALS uses their non-invasive ventilation for prolonged periods of time (e.g. >20 hours per day), cessation of non-invasive ventilation may be akin to ventilator withdrawal and can precipitate an acute change in respiratory status and a higher likelihood of the patient becoming acutely symptomatic when non-invasive ventilation is stopped. Such cases require special consideration as a form of withdrawal of life-sustaining therapies, if and when the patient decides to discontinue the use of non-invasive ventilation.

Question 6. What treatments reduce dyspnoea in advanced ALS?

As outlined above, ventilatory support initiated early in the disease trajectory can improve shortness of breath or dyspnoea. A number of other pharmacological and non-pharmacological interventions may also improve dyspnoea. Non-pharmacological interventions include circulation of air using a fan or an open window, and elevation of the head of the bed to relieve orthopnoea. Pharmacological management can be provided using opioids and benzodiazepines to reduce dyspnoea as ALS advances; however, there is little evidence to guide the dosing of these medications in ALS and so low, conservative doses should be used initially.

Take-home points are:

- Nutritional support using a gastrostomy tube may help alleviate weight loss and symptoms associated with dysphagia.
- Non-invasive ventilation initiated early in ALS is associated with benefits for quality of life and survival.

Advanced parkinsonism

Parkinson's disease is diagnosed when parkinsonism is seen without any clear cause. Parkinsonism is a clinical syndrome characterized by tremor, rigidity, slowed motor movements, and postural instability. Parkinson's disease is a neurodegenerative disorder that affects the motor system but also has many non-motor symptoms, including constipation, anxiety, depression, cognitive changes, and rapid eye movement (REM) sleep behaviour disorder, among others.[13] Parkinson's plus disorders include multiple system atrophy, progressive supranuclear palsy, Lewy body disease, and corticobasal degeneration.[13] Parkinson's plus disorders generally have a shorter survival than that seen with Parkinson's disease.

Case 24.3

P.D. is an 81-year-old man with advanced Parkinson's disease on dopaminergic therapy, admitted to hospital with aspiration pneumonia for the fourth time in 6 months. He is acutely hallucinating and shows evidence of a mixed hyperactive and hypoactive delirium. As a result of the delirium, he has been unable to take anything by mouth for the last 24 hours.

Question 7. What is the concern with Mr P.D. not being able to take his dopaminergic medication and how should that be approached?

In a person with Parkinson's disease who has been taking dopaminergic medications regularly, an abrupt cessation or withdrawal of the dopaminergic medication can put the person at risk of developing a neuroleptic malignant-like syndrome (also called parkinsonism hyperpyrexia syndrome or acute akinesia). Typical symptoms include mental status changes, muscle rigidity, fever, and autonomic instability (e.g. tachycardia and labile blood pressure). Laboratory findings may include elevated creatine kinase, lactate dehydrogenase, and liver transaminases, leucocytosis, and kidney impairment secondary to myoglobinuria.

The most important element in the management of neuroleptic malignant-like syndrome in Parkinson's disease is restoration of previous dopaminergic therapy. This can be accomplished by using a temporary nasogastric tube until the patient's swallowing improves sufficiently or using alternate administration routes such as the transdermal route (e.g. rotigotine patch—may exacerbate hallucinations). Supportive therapy should target the associated findings such as rhabdomyolysis, kidney impairment, fever, and electrolytes disturbances, among others. Benzodiazepines (e.g. lorazepam, diazepam) may be necessary, as part of the pharmacological management. The evidence base is poor, but dantrolene, bromocriptine, and amantadine have also been used in more severe cases or neuroleptic malignant syndrome.

In Mr P.D.'s case, the inability to swallow is likely secondary to the development of an acute delirium associated with aspiration pneumonia. This is a potentially reversible cause for the current inability to swallow. When formulating a treatment plan, it is important to keep in mind whether the recent rapid deterioration in swallowing may be reversible and possibly return to the patient's prior baseline, or is unlikely to return to normal after this hospitalization. In this case, strategies to overcome the temporary loss of the oral route, such as temporary insertion of a nasogastric tube, can be discussed with Mr P.D.'s substitute decision-maker while the underlying infection and delirium are treated.

Question 8. What should be taken into account when managing delirium in a person with Parkinson's disease or Parkinson's plus disorders?

The pharmacological management of delirium needs to be more carefully considered in people with Parkinson's disease or Parkinson's plus disorders. This is because the administration of antipsychotic medications with dopamine-blocking properties may cause significant worsening from a motor point of view and could potentially precipitate a neuroleptic malignant-like syndrome. The cornerstone of delirium management should be treatment of the underlying cause and elimination of medications that may be exacerbating the delirium, which may include some of the medications used to treat the underlying parkinsonism (e.g. dopamine receptor agonists). Any adjustments to the patient's dopaminergic medications should be made with careful consideration, as this may worsen a hypoactive delirium and also risks triggering the neuroleptic malignant-like syndrome.[14] Most antipsychotics should be avoided in parkinsonism, but quetiapine has a lower risk of extra-pyramidal side-effects and therefore may be considered if an antipsychotic medication is absolutely required for symptom management in delirium. Dosing of quetiapine should be kept low (e.g. 12.5–25 mg at bedtime) and titrated up slowly and only as required. Possible side-effects include hypotension, sedation, and worsening of motor function.[14]

Take home points are:

- Abrupt cessation of dopaminergic medications should be avoided in people with Parkinson's disease or related disorders.
- Antipsychotic medications with dopamine receptor-blocking properties should be avoided in people with Parkinson's disease or related disorders.

Multiple sclerosis

MS presents most frequently as a relapsing and remitting inflammatory disorder of the central nervous system that gradually changes over time to become a secondarily progressive disease with cumulative physical and cognitive impairments.[15] Symptoms in advanced MS are highly variable and include spasticity, gait impairment, urinary symptoms, psychosocial distress, ataxia, swallowing impairment, abnormal speech, and very commonly severe pain.

Case 24.4

P.R., a 67-year-old woman with a 25-year history of advanced MS (initially relapsing and remitting, then secondarily progressive), is seen in consultation. She is wheelchair-bound and has significant motor impairment in all four extremities that is related to both motor weakness and spasticity. Her gateway to the world is a tablet computer and she is able to use it by relying upon the limited function that remains in her right arm. She has burning and aching pain in all four extremities, worse in her buttocks and legs. She is seeking symptom management for her pain and she would like to be able to use her tablet more effectively.

Question 9. What types of pain does P.R. have? How will you approach pain management in this case?

The most common causes of pain in MS are central neuropathic pain, musculoskeletal pain, and mixed neuropathic and non-neuropathic pain.[16] Central neuropathic pain in MS is thought to occur because of demyelination in brain centres that perceive pain. Common symptoms include hyperalgesia, allodynia, and persistent burning pain.[16] A deep aching pain may also be reported as a form of neuropathic pain. Trigeminal neuralgia is another common cause of neuropathic pain in MS. Musculoskeletal pain in MS may be caused by spasticity, immobility, muscle spasms, and other causes seen in the general population such as osteoarthritis.

Distinguishing between neuropathic and musculoskeletal pain is important in order to determine the most appropriate approach for pain management. The first-line pharmacologic therapies for neuropathic pain management are gabapentinoids, tricyclic antidepressants, and serotonin–norepinephrine reuptake inhibitors[17] (see Table 24.4). When selecting which medication to prescribe for neuropathic pain, it is also helpful to consider the patient's comorbidities in an attempt to reduce the overall number of medications that may be required. Musculoskeletal pain, on the other hand, may benefit from a trial of acetaminophen or non-steroidal anti-inflammatory medication. In all cases, non-pharmacological management strategies such as physiotherapy for stretching and improving range of motion and massage therapy, among other approaches, may be helpful.[16]

In the case of Ms P.R., she has a combination of central neuropathic pain (burning aching pain in all four extremities) as well as musculoskeletal pain (buttock pain from prolonged periods of

Table 24.4 Evidence-based recommendations for pharmacological management of neuropathic pain

	Medication class	Specific examples
First-line therapy	Gabapentinoids	Gabapentin
		Pregabalin
	Tricyclic antidepressants	Nortriptyline
		Amitriptyline
	Serotonin–norepinephrine reuptake inhibitors	Duloxetine
		Venlafaxine
Second-line therapy	Tramadol	
	Other opioids	Morphine, hydromorphone, etc.
Third-line therapy	Cannabinoids	Dronabinol
		Tetrahydrocannabinol spray
		Medical marijuana
Fourth-line therapy	Anticonvulsants	Lamotrigine
	Methadone	
	Botulinum toxin	

Source: data from Moulin D, Boulanger et al. 'Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society'. Pain Res Manag, Vol. 19, Issue 6, pp.328–35.(2014) Hindawi Ltd.

time in the wheelchair). A medication could be prescribed for Ms P.R.'s neuropathic pain (as in Table 24.4), and rest periods out of the wheelchair throughout the daytime could be trialled, along with a reassessment of her seating and positioning to address the musculoskeletal pain.

Case 24.4 (continued)

P.R. states that muscle tightness in her right arm has been limiting her ability to use her tablet device in the last few months.

Question 10. What might be causing the loss of function in P.R.'s arm and how would you approach it?

Spasticity may contribute to musculoskeletal pain and impaired physical function. Physical examination of P.R., with special attention to muscle tone and reflexes in the upper extremities, will help determine whether spasticity is a contributor to the increasingly limited function in the right upper extremity. Once diagnosed, options for the treatment of spasticity should be assessed to improve quality of life. These include pharmacological (baclofen, tizanidine, botulinum toxin injections, oral tetrahydrocannabinol spray) and non-pharmacological (physiotherapy, stretching, appropriate seating, management of constipation and pressure sores) interventions. Oral pharmacological therapies are often best in the case of extensive spasticity, whereas botulinum toxin injections are more helpful for targeting specific muscle groups in localized spasticity and may have an added benefit of additional analgesia.

Important points are:

- An accurate diagnosis of pain (neuropathic versus musculoskeletal) and its anatomical source will help to guide the optimal treatment plan.
- Spasticity contributes to pain and motor dysfunction and should be managed both pharmacologically (oral medications, botulinum toxin injections) and non-pharmacologically (stretching, physiotherapy).

Seizures at the end of life

Case 24.5

M.G.K. is a 45-year-old man admitted to hospice with an advanced primary brain tumour. His presenting symptom at the time of diagnosis was a prolonged seizure, but the seizures had subsequently been well controlled using two oral anticonvulsant medications. However, since his admission, he has gradually lost the ability to swallow effectively and is now having frequent, self-limited focal seizures, without bilateral tonic–clonic movements or loss of consciousness, but with impaired awareness. His family approaches you because they are very concerned about the possibility of a generalized seizure similar to his initial presentation.

Question 11. What are the options for anticonvulsant prescribing at the end of life?

The most commonly prescribed route for anticonvulsants is by mouth. However, in people with advanced neurological illness or at the end of life, this is often no longer possible. An abrupt withdrawal of anticonvulsant therapy will increase the risk of seizure and status epilepticus, and so other routes for delivery of anticonvulsant medications need to be considered. In people for whom swallowing tablets is burdensome, many anticonvulsants are available as a liquid preparation or suspension (e.g. brivaracetam, carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, topiramate, valproate). Reasonable alternatives include the subcutaneous route (e.g. phenobarbital, midazolam, lorazepam, levetiracetam—growing body of evidence) and rectal route (e.g. carbamazepine, valproate, diazepam). Rectally administered preparations not commercially available may be available from a compounding pharmacy. Midazolam may also be administered either intranasally or as a buccal preparation with absorption via the oral mucosa.[19]

When the oral route for medication is lost at the end of life, seizure management is usually effectively achieved by switching to a subcutaneously administered anticonvulsant such as phenobarbital. However, a minority of people with difficult-to-control seizures will have recurrent seizures when anticonvulsant medications are changed. In these select patients, it may be necessary to continue the previously effective anticonvulsant or a combination of anticonvulsants in order to maintain seizure control.

Take-home points are:

- Anticonvulsants can be administered via multiple routes, even at the end of life.
- Maintenance of a previously effective medication regimen may be required in cases of particularly refractory seizures, even at the end of life.

Future directions

The field of palliative neurology or neuropalliative care is becoming increasingly recognized as a subspecialty of neurology and palliative medicine. Such expertise has emerged because neurologists and palliative care physicians alike have recognized the unique needs of people with neurological illnesses at the end of life. Continuing to integrate the expertise of palliative care physicians, neurologists, and neurosurgeons will enhance care for these complex patients.

References

1. **Gomez-Batiste X**, **Martinez-Munoz M**, **Blay C** *et al.* (2017) Utility of the NECPAL CCOMS-ICO((c)) tool and the Surprise Question as screening tools for early palliative care and to predict mortality in patients with advanced chronic conditions: a cohort study. *Palliat Med*, **31**, 754–63.
2. [**chapter authors**] (2017) Stroke. In: Aminoff M, Greenberg D, Simon RP (eds.) *Clinical Neurology*, 10th edn. McGraw-Hill, New York, NY.
3. **Canadian Stroke Best Practices**. *Nutrition and dysphagia*. https://www.strokebestpractices.ca
4. **Dennis MS**, **Lewis SC**, **Warlow C**, **Food Trial Collaboration** (2005) Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial. *Lancet*, **365**, 764–72.
5. **Ha L**, **Hauge T** (2003) Percutaneous endoscopic gastrostomy (PEG) for enteral nutrition in patients with stroke. *Scand J Gastroenterol*, **38**, 962–6.
6. **Blacquiere DP**, **Gubitz GJ**, **Dupere D**, **McLeod D**, **Phillips S** (2009) Evaluating an organized palliative care approach in patients with severe stroke. *Can J Neurol Sci*, **36**, 731–4.
7. **Ganzini L** (2006) Artificial nutrition and hydration at the end of life: ethics and evidence. *Palliat Support Care*, **4**(2), 135–43.
8. **O'Sullivan Maillet J**, **Baird Schwartz D**, **Posthauer ME**; **Academy of Nutrition and Dietetics** (2013) Position of the Academy of Nutrition and Dietetics: ethical and legal issues in feeding and hydration. *J Acad Nutr Diet*, **113**(6), 828–33. Erratum in: *J Acad Nutr Diet*, (2013) 113(12), 1759. Erratum in: *J Acad Nutr Diet*, (2013) 113(7), 985. Erratum in: *J Acad Nutr Diet*, (2017) 117(5), 808.
9. **Goutman SA** (2017) Diagnosis and clinical management of amyotrophic lateral sclerosis and other motor neuron disorders. *Continuum (Minneap Minn)*, **23**, 1332–59.
10. **Meunier CL**, **Malzahn AM**, **Boersma M** (2014) A new approach to homeostatic regulation: towards a unified view of physiological and ecological concepts. *PLoS One*, **9**, e107737.
11. **Miller RG**, **Jackson CE**, **Kasarskis EJ** *et al.* (2009) Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, **73**, 1227–33.
12. **Miller RG**, **Jackson CE**, **Kasarskis EJ** *et al.* (2009) Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, **73**, 1218–26.
13. [**chapter authors**] (2019) Movement disorders. In: Aminoff M, Greenberg D, Simon RP (eds.) *Clinical Neurology*, 10th edn. McGraw-Hill, New York, NY.
14. **Ebersbach G**, **Ip CW**, **Klebe S** *et al.* (2019) Management of delirium in Parkinson's disease. *J Neural Transm (Vienna)*.
15. **Krieger SC** (2016) New approaches to the diagnosis, clinical course, and goals of therapy in multiple sclerosis and related disorders. *Continuum (Minneap Minn)*, **22**, 723–9.
16. **Solaro C**, **Trabucco E**, **Messmer Uccelli M** (2013) Pain and multiple sclerosis: pathophysiology and treatment. *Curr Neurol Neurosci Rep*, **13**, 320.

17. **Moulin D**, **Boulanger A**, **Clark AJ** *et al*. (2014) Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manage*, **19**, 328–35.
18. **Johnston W**, **Simon J** (2012) Neurological disorders. In: Oneschuk D, Hagen N, MacDonald N (eds.) *Palliative Medicine: A Case-Based Manual*, 3rd edn, pp. 255–267. Oxford University Press, Oxford.

Chapter 25

Renal failure

Hasitha Welihinda

Attitude

To enable each learner to:

- Acquire the knowledge and skills required to manage symptoms related to kidney failure.
- Learn about the influence of chronic kidney disease on life expectancy.
- Consider the role of reduced-dose dialysis in patients not ready to discontinue dialysis.

Skills

To enable each learner to:

- Demonstrate skills needed to discuss the expected course of conservatively managed renal failure or dialysis discontinuation with patients and family.
- Diagnose and expertly manage symptoms related to renal failure, as well as other comorbid illness, taking into account reduced renal function.

Knowledge

To enable each learner to:

- Recognize the high mortality of patients treated with dialysis, including the effects of age and comorbidities.
- Describe appropriate selection of conservative care, dialysis discontinuation, and reduced dose dialysis.

Case 25.1

R.F. is an 85-year-old female with end-stage chronic kidney disease (CKD) who is being followed by nephrology in a multidisciplinary kidney clinic for her kidney failure. Her past medical history includes coronary artery disease and hypertension. The nephrologists believe her kidney disease is due to years of hypertension. Her blood pressure is well controlled on ramipril 10 mg po daily. She also takes metoprolol 25 mg po twice a day, rosuvastatin 10 mg po daily, and acetylsalicylic acid (ASA) 81 mg po daily.

Her estimated glomerular filtration rate (eGFR) is now 14 ml/minute, compared to 18 ml/minute a year earlier. She is managing all her activities of daily living independently and lives alone in a small apartment. She has three children nearby who help her with occasional shopping and doctor's appointments.

The nephrologists have recently been speaking with her and her family regarding what to do if the kidney disease progresses. They have brought up several options, including several forms of dialysis or managing the symptoms of kidney failure with medications (conservative management).

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Table 25.1 Chronic kidney disease stages

Chronic kidney disease stage	Glomerular filtration rate (ml/minute)
Stage 1	>90
Stage 2	60–90
Stage 3	30–59
Stage 4	15–29
Stage 5	<15

Source: data from Levey, A.S., et al., 'The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report'. Kidney Int, Vol. 80, Issue 1, pp. 17–28 (2011) Elsevier Inc.

Since you have been a long-time care provider for R.F., she has come to ask you about your opinion regarding her options.

Question 1. What is the prevalence of end-stage renal disease?

CKD has been increasing in prevalence due to an increase in risk factors, primarily increased rates of diabetes and vascular disease.[1] As age increases, the rates of contributing risk factors increase.[1] All stages (see Table 25.1) of CKD are more prevalent in the elderly.[1,2] There is also an increased disease burden in advanced CKD, with the majority of patients with CKD stages 4 and 5 having three or more serious comorbid conditions.[3]

The Canadian Institution for Health Information shows that R.F. is not alone and patients like R.F. (aged 75+) are the largest group of incident patients in the category of end-stage renal disease (ESRD).[5] It is very likely that a mixed practice will have many patients with similar conditions.

Question 2. How long can a patient like R.F. expect to live?

Life expectancy for individuals with CKD decreases with advancing age and advancing renal impairment. For a female with an eGFR of 15–29 ml/minute, survival is calculated to be 15.3 years if aged 30, but only 1.6 years if aged 85. The same 85-year-old female could be expected to live 3 years with an eGFR >60 ml/minute.[6] Another study looking at US data showed survival of 2.4 years in females older than 85 years with CKD, compared with 7.9 years in the general population.[7]

As R.F. now has an eGFR under 15 ml/minute, her life expectancy is likely months to short years.

Question 3. If dialysis were needed, how would the life expectancy of R.F. change?

Statistically, it is *unlikely* that R.F. will need to start dialysis. No matter the eGFR being considered, at age 85 and above, the likelihood of death exceeds the likelihood of needing to start dialysis (see Figure 25.1).[8]

Acute dialysis is considered under the situations listed below. Though no studies have directly examined this, if there is an indication for acute dialysis and it is *not* performed, then survival would be expected to be short ('hours to days').

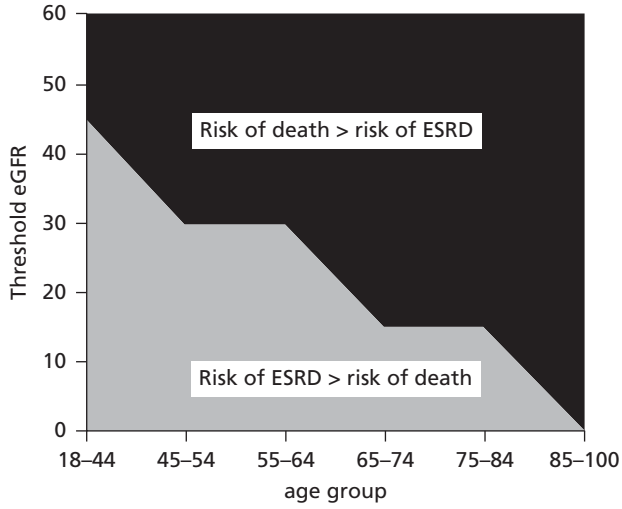


Fig. 25.1 Threshold eGFR versus age (starting dialysis versus risk of death).
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Acute dialysis indications

- Acidosis (not responsive to medical management).
- Electrolyte imbalances (such as hyperkalaemia not responsive to medical management).
- Ingestion of dialysable substances (such as ethylene glycol or lithium).
- Volume overload (not responsive to medical management).
- Uraemia complications (notably pericarditis or encephalopathy).

Dialysis can also be considered for individuals with progressive kidney disease who are at end-stage (usually eGFR <10 ml/minute) *and* have developed complications of renal failure such as difficult-to-control volume status or uraemic symptoms (see Box 25.1).[9] Low eGFR by itself is not considered an indication for dialysis initiation.[10]

In these chronic situations, several retrospective and prospective observational studies have looked at dialysis (versus conservative management) and survival. There are currently no published randomized controlled studies in this area. Available results suggest that for certain populations, there is no survival advantage, including:

- Individuals who are over 70 years of age and have a poor functional status.[12]
- Individuals who are over the age of 75 with ischaemic heart disease[13] or significant comorbidities.[12,14]
- Individuals who are over the age of 80.[12,14]

In addition, there was poor survival seen for those who reside in nursing homes, with a dramatic decline in functional status surrounding the initiation of dialysis.[15]

In studies where a small survival advantage was demonstrated for dialysis, the difference was offset by the number of days free of treatment and hospitalization.[16]

Box 25.1 Uraemic symptoms

- Fatigue
- Peripheral neuropathy
- Confusion
- Anorexia and nausea
- Changes in taste and smell
- Cramps
- Restless legs
- Sleep disturbance
- Itching
- Hiccups
- Sexual dysfunction
- Serositis
- Seizures
- Coma

Source data from Meyer, T.W. and T.H. Hostetter, 'Uremia'. (2007) N Engl J Med, Vol. 357, Issue 13, pp. 1316–25.

Several models have been proposed to predict dialysis mortality to aid when having goals of care discussions. The most popular uses the 'surprise question', serum albumin, age, and the presence of vascular disease or dementia to predict the 6-month mortality.[17]

If R.F. developed severe kidney failure in the future (e.g. due to sepsis-induced acute kidney injury), then her survival would be similar to that of individuals withdrawing from dialysis ('days to short weeks'). It could be even shorter due to the precipitating illness (sepsis in the previous example) or the development of an indication for acute dialysis (hyperkalaemia).

However, if someone like her had slowly progressive CKD, average survival would likely be similar, whether dialysis was initiated or not. Conservative management may be a good option for her if she wishes to minimize healthcare visits.

Case 25.1 (continued)

R.F.'s family has noticed that she has become a bit more forgetful over the past 2 years. In their research about kidney failure, they read about uraemic encephalopathy (cognitive changes caused by build-up of uraemic toxins). They are wondering if her forgetfulness is due to kidney failure and whether dialysis would improve this.

Question 4. When can we expect symptoms due to renal failure?

The majority of symptoms due to renal failure can be classified into four categories:

1. Symptoms due to accumulation of volume (fluid): this can occur at any level of renal failure if the dietary sodium load is greater than the kidney's ability to excrete. This leads to volume

accumulation which can cause symptoms, depending on the body compartment in which the fluid collects (i.e. fluid accumulation in the lungs can lead to pulmonary oedema or a pleural effusion which can cause dyspnoea).

2. Symptoms due to elevated levels of phosphate and parathyroid hormone (PTH): this can lead to worsening pruritus, though levels have to be dramatically elevated. These elevations can occur as early as when eGFR is below 60 ml/minute but usually requires more significant renal impairment.[18]
3. Symptoms of renal anaemia: usually occurs at eGFR below 30 ml/minute but can occur at higher levels in individuals with diabetes and those with inflammatory diseases.[18]
4. Symptoms due to accumulation of 'uraemic toxins': these are the unmeasured by-products of metabolism that lead to the clinical syndrome of uraemia. It is not due to elevation in the levels of urea (azotaemia). This generally occurs when eGFR is 5–10 ml/minute but can, on occasion, occur outside this range.[10]

Much like R.F. and her family, patients and family members often have questions regarding if symptoms are due to renal failure. This is particularly difficult to tease out when renal function is low and comorbid disease is also present. For example, in a patient where kidney and heart failure coexist, it can be difficult to determine if symptoms such as fatigue or dyspnoea are due to the kidney disease, heart disease, or a combination of both.

Given that R.F.'s symptoms were present when her renal function was not low enough to be a likely cause of her cognitive issues, it is unlikely that her memory issues are due to her renal failure.

Case 25.1 (continued)

R.F. is wondering if there is anything she can do to improve her kidney function or delay the need for dialysis.

Question 5. What interventions can you offer R.F. to potentially slow the rate of renal decline?

There is some debate about the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in advanced CKD. Current evidence suggests they be continued due to cardiovascular benefits, given the high rates of cardiovascular disease in this population. However, there are wide practice patterns, with some nephrologists discontinuing ACEIs at very advanced levels of CKD to allow renal autoregulation to resume, and thereby potentially improve the glomerular filtration rate (GFR). This usually allows for more time before dialysis initiation. In individuals wishing to pursue conservative management, this may be a strong consideration.[19]

Studies looking at dietary choices have shown that reduced dietary protein intake was associated with a slower progression of kidney disease.[20] In addition, lower protein intake has been shown to reduce the severity of uraemic symptoms.[21] Despite these studies, recommendation of a reduced protein diet remains controversial in the general kidney disease population due to the prevalence of malnutrition and associated morbidity.[20] If implemented with close monitoring, it may be a consideration for individuals wishing to make dietary changes to slow progression and manage symptoms.[22]

Case 25.1 (continued)

You recommend R.F. discontinue her ramipril and change to amlodipine to keep her blood pressure within target. A few weeks later, repeat labs show that her renal function has stabilized at around 20 ml/minute. She

is concerned about weight loss and is finding it difficult to eat enough calories. A dietitian consult is arranged. You collectively conclude that a lower-protein diet would not be appropriate for her.

Case 25.2

J.K. is a 45-year-old male with kidney failure due to type 1 diabetes who has been on dialysis for the past 15 years. He has had numerous complications from his diabetes, including bilateral below-knee amputations due to peripheral vascular disease. He has had diabetic neuropathy which predisposes him to ulcers. He has severe pain in both lower extremities, including phantom limb pain. He has worsening diabetic retinopathy. He is now considered legally blind.

He is unhappy with his quality of life and is considering stopping dialysis. He is aware of the option in Canada of medical assistance in dying; however, he does not wish to pursue it.

Question 6. How long will J.K. survive without dialysis?

Most texts on dialysis withdrawal suggest an average survival of days to short weeks. Death can occur due to any of the complications of renal failure. Early on, the main cause of death is usually cardiac arrhythmias due to electrolyte abnormalities. Late death can be due to many causes, including accumulation of 'uraemic toxins' which is closely tied to nutritional intake, metabolism, and residual renal function (RRF). Although average survival is measured in days to short weeks, the literature has reported a wide range of timings for death following dialysis discontinuation, with survival reported of up to 150 days.[23,24]

In J.K.'s case, it will be important to ask about his RRF. Some individuals on dialysis produce up to 500 ml (or more) of urine per day, while others are anuric. It should be explained to J.K. and his family that upon discontinuing dialysis, the average survival is days to short weeks, but death can occur at any time. They should also know that rarely it can take short months, especially in individuals with significant RRF (urine production can usually be used as a surrogate, as the RRF is not easily measured while on dialysis and will be different from serum creatinine/eGFR values measured while on dialysis or shortly after discontinuation).

Question 7. How is pain management different for patients with renal failure?

Pain management in renal failure is similar to what has been described previously, with the following caveats. Attention should be paid to avoidance of nephrotoxic medications. The main category is non-steroidal anti-inflammatory drugs (NSAIDs) which will reduce any RRF the patient may have (the RRF is associated with survival benefit). NSAIDs can be considered in select patients with minimal RRF and no history of active coronary artery disease or gastritis/ulcers. Acetaminophen is the preferred agent for non-opioid pain medication.[25]

Adjuvants such as tricyclic antidepressants (TCAs) do not need dosing adjustments, though they should be closely monitored as metabolites are renally cleared. Some medications, such as gabapentin or pregabalin, require renal dosing adjustments and will need to be discontinued if dialysis is discontinued. Others such as baclofen are contraindicated, even in individuals receiving scheduled dialysis.[25] If in doubt, you should ask for assistance from your pharmacist.

If the above two approaches do not control symptoms appropriately, an opioid can be considered, as per the World Health Organization (WHO) pain ladder.[26] Though fentanyl and methadone are the only two opioids with no active metabolites which require renal clearance, difficulties in dose adjustment and delivery make their use in an outpatient setting more challenging. Of the remaining opioids, the preferred agent is hydromorphone which can be given via the oral or parenteral route. Many practitioners prefer to rotate to fentanyl if dialysis is discontinued or if higher doses of hydromorphone are required, due to concerns regarding accumulation of metabolites.[25]

Question 8. What symptoms can J.K. expect once dialysis is stopped and how can they be managed?

The classic description of death from uraemia is a peaceful and drowsy state, much like falling asleep. Looking at the literature, however, it is clear that many individuals discontinuing dialysis treatment become symptomatic in the last hours to days of their life.[24] It is therefore essential that there is a clear treatment plan and an understanding of who will be providing symptom management, should it become necessary.

One study following 79 individuals discontinuing dialysis found that in the last 24 hours, the most common symptoms experienced included pain (42%), agitation (30%), myoclonus (28%), dyspnoea (25%), and nausea (13%).[24] Providers should have a good understanding of the management of these symptoms in renal failure (see Table 25.2).

Table 25.2 Management of common dialysis discontinuation symptoms at end of life

Nausea	
Uraemic toxins—chemoreceptor trigger zone	
Haldol	Start at half the normal dose
Methotrimeprazine	Can be considered if Haldol® ineffective
Encephalopathy/agitation	
Uraemic toxins/delirium	
Haldol®	Recommended treatment
Midazolam	Used for severe agitation but can cause excess sedation
Methotrimeprazine	Use has been described in literature
Dyspnoea	
Volume overload/metabolic acidosis	
Opioids:	
Hydromorphone	Can be considered if use will only be short term
Fentanyl	Continuous infusion usually required due to short half-life
Non-medical interventions	Fans/positioning/relaxation techniques/etc.
If survival is days to weeks or longer consider:	
Sodium bicarbonate	To improve symptoms of breathlessness due to acidosis
Furosemide	Consider diuresis if significant residual renal function present

Source: data from Raghavan, D. and J.L. Holley, 'Conservative Care of the Elderly CKD Patient: A Practical Guide'. Adv Chronic Kidney Dis, Vol. 23, Issue 1, pp. 51–6. (2016) Elsevier Ltd.

Case 25.3

G.D. is a 73-year-old male with kidney failure from hypertension and type 2 diabetes who has been on haemodialysis for 5 years. His dialysis treatments have been stable and incident-free. He receives 4-hour treatments, three times per week. His nephrologist has been very satisfied with his toxin clearance, electrolyte stability, and volume management.

Four months ago, he was newly diagnosed with metastatic lung cancer and has decided not to undergo any disease-directed treatments such as chemotherapy or radiation. Over the past month, he has noticed a significant decrease in his functional status and energy levels. He now finds it difficult to manage his activities of daily living. His appetite is reduced, and he has lost 5 kg in the past month.

He lives 2 hours away from the dialysis centre in an apartment with his wife. She has started to manage household affairs and drives him to his appointments, including dialysis treatments.

He is finding it difficult to come to dialysis but does not wish to stop at this point.

Question 9. What modifications could be made to his dialysis prescription to improve his quality of life?

Dialysis is prescribed to replace lost native kidney function. Initial studies looked at the dialysis dose required to avoid uraemic symptoms. These studies had only a few elderly patients whose metabolic rates/protein consumption, and theoretically uraemic toxin generation, differ from younger patients. Current guidelines were developed using these previously determined doses, with an added safety margin, which strive to improve long-term outcomes.[28]

Dialysis requirements in the elderly have not been rigorously studied, but many dialysis centres do offer reduced dose dialysis to individuals who have limited life expectancy. The goals of reduced dose dialysis is to correct short-term measures indicating dialysis adequacy, which can be problematic in days to weeks if left unchecked.[29]

Examples of short-term measures of dialysis adequacy include:

- Control of fluid balance (stable weight/oedema/blood pressure).
- Control of electrolytes (stable serum potassium).
- Control of acid/base balance in the body.
- Avoidance of uraemic encephalopathy.

Examples of long-term measures of dialysis adequacy (may take years to become problematic) include:

- Prevention of dialysis-associated amyloid.
- Improved cardiovascular survival.

Case 25.3 (continued)

You arrange for a family meeting with G.D., his wife, and the nephrology team who change his dialysis to twice weekly. As his functional status and oral intake deteriorate, his dialysis dose is changed to once weekly, with extra sessions as required for volume control.

Question 10. Is it possible to safely decrease the frequency of someone's dialysis?

It is possible to decrease the frequency of dialysis targeting the short term measures of dialysis adequacy described above. As this does not address long term measures of dialysis adequacy, this

reduction is likely not appropriate in those who have life expectancy greater than several months to years (depending on the degree of reduction). As oral intake decreases, patients reach a point where weekly potassium and fluid intake can be removed in one dialysis session. Therefore in a select group of dialysis recipients with short life expectancy, this type of dialysis may prolong survival but not be as burdensome as the standard three times per week prescription, and may not cause any significant complications due to the reduced dose over their limited lifetime.

Case 25.3 (continued)

Two weeks later, G.D. begins to develop mild uraemic symptoms. His main complaint is nausea, and low-dose haloperidol is added to his treatment plan.

A month later, his functional status keeps him mainly in bed and he decides to withdraw from dialysis completely and makes plans for end-of-life care to be provided at home. You arrange for the appropriate medications to be sent to his home.

References

1. **Williams ME**, **Sandeep J**, **Catic A** (2012) Aging and ESRD demographics: consequences for the practice of dialysis. *Semin Dial*, **25**(6), 617–22.
2. **Berman N** (2014) End-of-life matters in chronic renal failure. *Curr Opin Support Palliat Care*, **8**(4), 371–7.
3. Bello AK, Ronksley PE, Tangri N *et al.* (2019) Prevalence and demographics of CKD in Canadian primary care practices: a cross-sectional Study. *Kidney Int Rep*, **4**(4), 561–70.
4. **Levey AS**, de Jong PE, Coresh J *et al.* (2011) The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*, **80**(1), 17–28.
5. **Canadian Institute for Health Information** (2019) *Treatment of end-stage organ failure in Canada, Canadian Organ Replacement Register, 2007 to 2016: data tables, end-stage kidney disease and kidney transplants*. https://www.cihi.ca/sites/default/files/document/corr_ar-kidney-data-tables-en.xlsx
6. Turin TC, Tonelli M, Manns BJ *et al.* (2012) Chronic kidney disease and life expectancy. *Nephrol Dial Transplant*, **27**(8), 3182–6.
7. **Neild GH** (2017) Life expectancy with chronic kidney disease: an educational review. *Pediatr Nephrol (Berlin)*, **32**(2), 243–8.
8. **Germain MJ**, **Cohen LM** (2008) Maintaining quality of life at the end of life in the end-stage renal disease population. *Adv Chronic Kidney Dis*, **15**(2), 133–9.
9. **Brown EA**, **Johansson L** (2011) Epidemiology and management of end-stage renal disease in the elderly. *Nat Rev Nephrol*, **7**(10), 591–8.
10. Levin A, Stevens PE, Bilous RW *et al.* (2013) Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*, **3**(1), 1–150.
11. **Meyer TW**, **Hostetter TH** (2007) Uremia. *N Engl J Med*, **357**(13), 1316–25.
12. **Hussain JA**, **Mooney A**, **Russon L** (2013) Comparison of survival analysis and palliative care involvement in patients aged over 70 years choosing conservative management or renal replacement therapy in advanced chronic kidney disease. *Palliat Med*, **27**(9), 829–39.
13. Murtagh FE, Marsh JE, Donohoe P *et al.* (2007) Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. *Nephrol Dial Transplant*, **22**(7), 1955–62.
14. Verberne WR, Geers AB, Jellema WT *et al.* (2016) Comparative survival among older adults with advanced kidney disease managed conservatively versus with dialysis. *Clin J Am Soc Nephrol*, **11**(4), 633–40.

15. Kurella Tamura M, Covinsky KE, Chertow GM *et al.* (2009) Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med*, **361**(16), 1539–47.
16. Carson RC, Juszczak M, Davenport A *et al.* (2009) Is maximum conservative management an equivalent treatment option to dialysis for elderly patients with significant comorbid disease? *Clin J Am Soc Nephrol*, **4**(10), 1611–19.
17. Cohen LM, Ruthazer R, Moss AH *et al.* (2010) Predicting six-month mortality for patients who are on maintenance hemodialysis. *Clin J Am Soc Nephrol*, **5**(1), 72–9.
18. **Ng BL**, **Anpalahan M** (2011) Management of chronic kidney disease in the elderly. *Intern Med J*, **41**(11), 761–8.
19. **Ahmed A**, **Jorna T**, **Bhandari S** (2016) Should we STOP angiotensin converting enzyme inhibitors/angiotensin receptor blockers in advanced kidney disease? *Nephron*, **133**(3), 147–58.
20. Metzger M, Yuan WL, Haymann JP *et al.* (2017) Association of a low-protein diet with slower progression of CKD. *Kidney Int Rep*, **3**(1), 105–14.
21. Aparicio M, Bellizzi V, Chauveau P *et al.* (2012) Protein-restricted diets plus keto/amino acids—a valid therapeutic approach for chronic kidney disease patients. *J Ren Nutr*, **22**(2 Suppl), S1–21.
22. **Kurella Tamura M** (2009) Incidence, management, and outcomes of end-stage renal disease in the elderly. *Curr Opin Nephrol Hypertens*, **18**(3), 252–7.
23. O'Connor NR, Dougherty M, Harris PS *et al.* (2013) Survival after dialysis discontinuation and hospice enrollment for ESRD. *Clin J Am Soc Nephrol*, **8**(12), 2117–22.
24. Cohen LM, Germain M, Poppel DM *et al.* (2000) Dialysis discontinuation and palliative care. *Am J Kidney Dis*, **36**(1), 140–4.
25. **O'Connor NR**, **Corcoran AM** (2012) End-stage renal disease: symptom management and advance care planning. *Am Fam Physician*, **85**(7), 705–10.
26. **Pham PC**, Khaing K, Sievers TM *et al.* (2017) 2017 update on pain management in patients with chronic kidney disease. *Clin Kidney J*, **10**(5), 688–97.
27. **Raghavan D**, **Holley JL** (2016) Conservative care of the elderly CKD patient: a practical guide. *Adv Chronic Kidney Dis*, **23**(1), 51–6.
28. Scribner BH, Cole JJ, Ahmad S *et al.* (2004) Why thrice weekly dialysis? *Hemodial Int*, **8**(2), 188–92.
29. Obi Y, Eriguchi R, Ou SM *et al.* (2015) What is known and unknown about twice-weekly hemodialysis. *Blood Purif*, **40**(4), 298–305.

Chapter 26

Cirrhosis and diseases of the gastrointestinal tract

Tim Hiebert

Attitude

To enable each learner to:

- Recognize the importance of a palliative approach in end-stage liver disease (ESLD) and other diseases of the gastrointestinal (GI) tract.
- Recognize the impact of stigma in patients with cirrhosis and other diseases commonly associated with 'lifestyle'.

Skills

To enable each learner to:

- Assess the symptoms of ESLD and other GI disorders.
- Generate a treatment plan for the most common symptoms, including ascites, hepatic encephalopathy (HE), pruritus, nausea, and pain.
- Enable sensitive and compassionate care.

Knowledge

To enable each learner to:

- Understand the pathophysiology of cirrhosis and other life-threatening diseases of the GI tract.
- Be aware of the major complications of cirrhosis.
- Understand the difficulties of pharmacotherapy in liver dysfunction.

Case 26.1

G.B. is a 47-year-old male with cirrhosis for 9 years. He has a history of chronic hepatitis B diagnosed 13 years ago. He received interferon therapy, which he did not tolerate due to adverse effects. Past medical history includes massive haemorrhage due to injuries sustained in a motor vehicle accident at the age of 14 requiring large-volume red cell transfusion. He consumed alcohol socially until his diagnosis of cirrhosis and has abstained completely since then. He is in a long-standing, stable, monogamous same-sex relationship. He is currently unemployed and has long-standing financial struggles and chronic anxiety. His medications include citalopram and antiviral therapy for his chronic hepatitis.

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Question 1. What are the common causes of cirrhosis? What is the impact of end-stage liver disease?

Cirrhosis is the irreversible result of ongoing inflammation and fibrosis of the liver. Aetiologies of ESLD include chronic viral hepatitis (B and C), non-alcoholic fatty liver disease, alcoholic liver disease, haemochromatosis, cystic fibrosis, primary sclerosing cholangitis, primary biliary cirrhosis, and advanced heart disease.[1] Progressive loss of liver function and significant mortality and morbidity arise in all of these disorders. Major complications include ascites, spontaneous bacterial peritonitis (SBP), HE, hepatorenal syndrome, hepatocellular carcinoma, and hepatopulmonary syndrome.[1] ESLD symptoms include pain, dyspnoea, pruritus, fatigue, sleep disturbances, cramps, sexual dysfunction, depression, and anxiety.[2] Symptom severity is similar to other advanced diseases, including advanced cancers.[2] Both the general population and healthcare community often view cirrhosis as primarily related to alcohol abuse or intravenous (IV) drug use, and patients with ESLD experience stigma.[3] In Canada, cirrhosis is the tenth leading cause of death, with more than 3000 victims annually,[4] and is the eighth leading cause of death in the United States.[5] While ESLD is a terminal condition, this is often not recognized and treatment is often highly focused on life prolongation and transplantation. Unfortunately, many patients with ESLD are not transplant candidates or will die awaiting transplant.[6]

Case 26.1 (continued)

G.B. presents to the emergency department with abdominal distension and abdominal pain. He reports nausea, diminished oral intake, and shortness of breath on exertion. Investigations reveal mildly elevated transaminases, bilirubin 35 μmol/l, international normalized ratio (INR) 2.1, creatinine (Cr) 107 μmol/l, and albumin 21 g/l. Ultrasound of the abdomen shows an echogenic liver, portal hypertension, gastric varices, splenomegaly, and large ascites. He receives a large-volume paracentesis (LVP), which he tolerates well. He is prescribed furosemide, spironolactone, and a low-salt diet. Follow-up is arranged with his hepatologist.

Question 2. How advanced is G.B.'s illness?

Patients with compensated cirrhosis have a median life expectancy of 12 years.[7] Cirrhosis is categorized as compensated or decompensated, depending on the absence or presence of major complications named earlier.[1] Decompensated cirrhosis portends a median survival of 2 years.[1] While individual variability is great, prognostic tools can be very useful. The Child–Pugh (CP) score (Table 26.1) and the Model for End-stage Liver Disease (MELD) equation, which incorporates

Table 26.1 Summary of the Child–Pugh classification

Parameter	1 point	2 points	3 points
Albumin (g/l)	>35	28–35	<28
Ascites	None	Minimal	Moderate/severe
Bilirubin (μmol/l)	<34.2	34.2–51.3	>51.3
Encephalopathy	Absent	Grades 1–2	Grades 3–4
INR	<1.7	1.7–2.3	>2.3

Source: data from Child CG, Turcotte JG. 'Surgery and Portal Hypertension'. In: The Liver and portal hypertension, Child CG III (Ed), WB Saunders, Philadelphia 19649 and Pugh RN, et al. 'Transection of the oesophagus for bleeding oesophageal varices'. Br J Surg. Vol. 60, Issue 8, pp. 646–9. (1973) John Wiley & Sons10

Table 26.2 Child–Pugh class and prognosis

Child–Pugh class	Points	One-year survival (%)
A	5–6	100
B	7–9	80
C	10–15	45

Source: data from Pugh RN, et al. 'Transection of the oesophagus for bleeding oesophageal varices'. Br J Surg. Vol. 60, Issue 8, pp. 646–9. (1973) John Wiley & Sons10

serum bilirubin, Cr, and INR, are the most common tools.[8] The CP score uses bilirubin, albumin, and INR values, together with the presence and severity of encephalopathy and ascites. A CP score of ≥12 and MELD ≥21 are both associated with a prognosis of less than 6 months.[8,9,10] Rapidly progressive hepatorenal syndrome, intensive care admission, refractory ascites, and encephalopathy all portend a shorter prognosis.[8] With the development of overt ascites, G.B. now has decompensated cirrhosis with a CP score of 10 (grade C) and a MELD score of <21 and his life expectancy is likely less than 2 years without liver transplant. CP grades of A, B, and C are associated with 1-year survival of 100, 85, and 45%, respectively[8,10,11] (Table 26.2).

Question 3. What treatment options are appropriate to manage Mr G.B.'s ascites?

Ascites, the pathologic accumulation of peritoneal fluid, is the most common complication of cirrhosis, arising in 5–10% of patients annually and in approximately 50% over 10 years.[12] It is associated with worsened quality of life.[13] Mechanisms underlying ascites in cirrhosis are complex but are primarily the result of portal hypertension and intense activation of the renin–angiotensin–aldosterone system, antidiuretic hormone, and splanchnic vasodilation.[14] Patients with ascites suffer from abdominal fullness, dyspnoea, early satiety, abdominal pain and nausea ~~(Day 2015)~~,[2,6] and a risk of SBP.

When suspecting ascites, one should enquire about the above, as well as increasing abdominal girth, lower extremity oedema, and weight gain.[15] On examination, bulging flanks, flank dullness, shifting dullness, and a fluid wave are all useful for 'ruling in' ascites.[15] Abdominal ultrasound is a non-invasive, sensitive, and specific confirmatory test.[16] In order to confirm cirrhosis as the cause of ascites, a diagnostic paracentesis should be performed at least once for cell count, albumin, total protein, and culture. The serum ascites albumin gradient (SAAG) should be measured.[14] A SAAG >11 g/l reliably diagnoses ascites due to portal hypertension.[17]

Sodium restriction of less than 2 g/day is the mainstay of therapy for cirrhotic ascites. Unfortunately, this very bland diet is poorly tolerated and only successful in managing ascites in 10% of patients.[14] Additional treatment includes the diuretics spironolactone and furosemide in a 100 mg/40 mg ratio.[18] Ascites is considered to be diuretic-refractory when it cannot be controlled with 400 mg/160 mg spironolactone/furosemide ratio and a salt-restricted diet. Diuretic-refractory ascites is usually treated with serial paracentesis. LVP as needed is well tolerated by most patients.[14] Albumin transfusion for LVP >5 litres is reasonable.[17] Blood work is not required prior to paracentesis, as anaemia, coagulopathy, and thrombocytopenia are not contraindications. Patients should be monitored closely throughout the procedure, and drainage aborted at any sign of difficulty. If point-of-care ultrasound guidance is available, it provides an extra layer of procedural safety.[19] Paracentesis can be safely performed in the patient's home as well.[17] For selected patients, a permanent indwelling tunnelled peritoneal catheter allows for

routine drainage of peritoneal fluid at any time and preliminary data reveal low complication rates.[20] Non-tunnelled catheters, such as a 'pig-tail', should only be considered for short-term drainage. Other treatments of refractory ascites include insertion of a transjugular intrahepatic portosystemic shunt (TIPS) which reduces portal pressure and decreases ascites production. TIPS is invasive and associated with an increased incidence of severe HE.[14] Peritoneovenous shunts (PVS) are infrequently performed and are associated with multiple complications, particularly infection.[17]

Case 26.1 (continued)

G.B. is discharged on a combination of spironolactone/furosemide 200 mg/80 mg daily and a sodium-restricted diet. His ascites and peripheral oedema improve. He returns to his hepatologist to discuss his severe liver disease and possible liver transplantation. Goals of care are explored and G.B. indicates a strong desire to pursue all possible life-sustaining therapies. Pre-transplant assessments are performed. He is identified as a potential liver transplant candidate.

Question 4. Is there a role for palliative care in the care of patients with ESLD while awaiting liver transplant?

YES!

The incorporation of a palliative approach to care for patients with other end-organ diseases, including chronic obstructive pulmonary disease (COPD) and end-stage heart and renal diseases, has shown multiple benefits and is recommended in the guidelines of several major medical societies.[6] Quality of life in ESLD is linked to potentially treatable symptoms.[13] The symptom burden of ESLD is similar to that in patients with advanced cancer.[2] Patients awaiting transplant have decompensated disease by definition. Simultaneous transplant assessment and enrolment in outpatient hospice programmes have shown to be beneficial and were not an impediment to subsequent transplant.[21] A surgical intensive care unit (ICU) intervention, incorporating early palliative care integration and a communication bundle, dramatically increased the frequency of goals of care discussions, increased rates of 'Do Not Attempt Resuscitation' (DNAR) status, showed earlier withdrawal of life-sustaining therapies, but no change in survival, and gave 'families more time to prepare'.[22]

Unfortunately, palliative care for ESLD is provided infrequently and is not recommended by any major medical society.[6] In a large US study, referral to palliative care among inpatients with ESLD was only 1% in 2006 and 7% in 2012.[23] Numerous barriers exist, the most pervasive barrier being 'the allure of transplant' which offers an excellent chance at survival for selected patients.[6] This hope often leads to an intense focus on life-sustaining therapies only.[24] The variable course of ESLD creates difficulties in determining the timing of palliative referrals[6] and many physicians view palliative care as appropriate only at the very end of life.[24] Race, socio-economic status, and provider bias may influence the likelihood of palliative care referral.[6]

Case 26.1 (continued)

Over several months, G.B. develops muscle cramps, fatigue, mood changes, and sleep disturbance. Additionally, he experiences more complications of advanced liver disease, including an episode of SBP, and his hospitalization is prolonged by delirium and HE. He was treated with lactulose and ceftriaxone and discharged 3 weeks later with significant functional losses, the addition of lactulose three times a day, and

prophylactic ciprofloxacin for SBP prophylaxis. He remains hopeful that a liver transplant is on the horizon and G.B. persists in desiring aggressive medical care.

Question 5. What treatments are effective to reduce pruritus and hepatic encephalopathy?

Pruritus

A Greek physician Aretaeus the Cappadocian recognized the association between jaundice and itch nearly 2000 years ago.[25] Factors contributing to pruritus include bile acids, other accumulating pruritogens, endogenous opioids, histamine, and serotonin.[25] Itch is most frequently associated with primary biliary cholangitis, primary sclerosing cholangitis, and other cholestatic diseases but can arise with cirrhosis of any cause. It may be localized or generalized. Pruritus is frequently underappreciated by care providers. Non-pharmacologic treatments include topical emollients, cool baths, and avoidance of products that dry the skin. Scented soaps and lotions and medications known to cause itch should be avoided. Patients with obstructive jaundice from mechanical causes can be considered for interventions, including percutaneous biliary drainage. For primary biliary cholangitis, ursodeoxycholic acid is a recommended treatment.[25] Recommended pharmacologic measures include anion exchange resins (cholestyramine), rifampicin, sertraline, naltrexone, and antihistamines.[25] Methylnaltrexone has been effective in case reports of cholestatic pruritus.[26] Serotonin receptor antagonists are often ineffective.[27]

Hepatic encephalopathy

HE is a form of potentially reversible brain dysfunction caused by severe liver dysfunction. It frequently occurs in advanced liver disease. The mechanisms of HE are multifactorial and poorly understood.[28,29] The primary driver is thought to be increased levels of ammonia in the serum due to impaired liver function and shunting around the liver.[29]

The severity of HE is staged from minimal up to stage IV (Table 26.3).[29] Minimal and stage I are covert hepatic encephalopathy (CHE), while stages II and above are labelled as overt hepatic encephalopathy (OHE). CHE may arise in up to 80% of patients with decompensated cirrhosis, and OHE in 30–40%.[29] CHE is difficult to identify, with subtle changes in cognitive function and personality, and often requires psychometric testing for diagnosis.[29] CHE invariably precedes episodes of OHE.[29] Disorientation and asterixis are accepted as the dividing line between CHE and OHE.[29] Asterixis is not tremor, but an involuntary flapping motion of dorsiflexed hands, and reflects the inability to maintain a posture.[29] OHE manifests with lethargy, disorientations, and, when more severe, somnolence, bizarre behaviour, and ultimately coma.[29,30] Other neurologic findings in HE include positive Babinski sign, hypo- or hyper-reflexia, tremor, bradykinesia, and rigidity.[29]

Non-absorbable disaccharides, usually lactulose, are the first-line therapy for both CHE and OHE, acting to increase ammonia excretion.[31] Lactulose is, however, associated with abdominal cramping, flatulence, diarrhoea, patient discomfort, and diminished adherence. Polyethylene glycol (PEG) has also been found to be an effective treatment for HE[29] but has only been studied in very high doses, which may not be acceptable to all patients. Treatment should also include optimal nutrition and, contrary to prior belief, a diet rich in protein. Probiotics also provide some benefit.[31] Rifaximin is a non-absorbable oral antibiotic which alters gut flora, thereby increasing ammonia excretion. While other oral antibiotics are used 'off-label' to treat HE, rifaximin has

Table 26.3 Summary of hepatic encephalopathy staging

Stage of hepatic encephalopathy	Clinical features	
Minimal	Deficits on psychometric testing	Covert
Stage I	Minor changes in cognition, behavioural changes, and altered sleep patterns	
Stage II	Lethargy or apathy, disorientation, personality changes, overt asterixis	Overt
Stage III	Somnolence, grossly confused, bizarre behaviour, overt asterixis	
Stage IV	Coma	

Source: data from Vilstrup H, et al. 'Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver'. Hepatology. Vol. 60, Issue 2, pp.715-35. (2014) John Wiley & Sons;[29] and Bajaj JS, et al. 'Spectrum of neurocognitive impairment in cirrhosis: Implications for the assessment of hepatic encephalopathy'. Hepatology. Vol. 50, Issue 6, pp.2014-21 (2009) John Wiley & Sons.[31]

shown a clear benefit, either in addition to lactulose or as monotherapy.[31] For OHE, the precipitant should be treated (in G.B.'s case SBP). Triggers include infections such as SBP, GI bleeding, electrolyte disturbances, hypovolaemia, constipation, medications, acute portal or hepatic vein occlusion, and hepatocellular carcinoma. Opioids, benzodiazepines, and other sedating medications are of particular concern. Alternative diagnoses should also be considered. The differential diagnosis for HE is very long and includes all potential causes of delirium and acute confusional states. Measuring serum ammonia levels is of dubious utility.[29] Therefore, medication review, as well as detailed history and assessment, are essential.

Severe HE is life-threatening and treatment choices should be considered carefully. In patients who are potential candidates for liver transplant, a very aggressive approach, including ICU admission, intubation, and nasogastic tube placement for enteral lactulose administration, may be warranted. For others, these treatments may only serve to prolong suffering. The importance of advance care planning (ACP) and ensuring that treatment decisions align with both clinical realities and patient values cannot be overstated.

Case 26.1 (continued)

G.B. has a series of healthcare encounters where he is repeatedly asked questions such as 'Are you still drinking?' and 'It is important to be honest!'. He has overheard members of the healthcare team speak disparagingly of patients with alcoholism and substance use disorder. When he was in pain, nurses appeared hesitant to provide pain medications. The development of clinical ascites made G.B.'s liver disease obvious to members of his social circle and family. He feels judged by others for bringing his disease on himself. G.B. has become suspicious of care providers and feels increasingly isolated.

Question 6. What is stigma? How does stigma affect patients with ESLD?

Stigma is the experience of disgrace associated with a person's identity or circumstances.[32] This disgraced status can have a profound negative effect on a patient. Stigmatization is well documented for patients with so-called 'lifestyle-related' illnesses such as addiction and human

immunodeficiency virus (HIV).[3] Stigmatization can lead to diminished quality of life, isolation, depression, distrust of healthcare providers, and reduced adherence to treatments and may be associated with decreased medical access.[3,6] Individuals with ESLD, regardless of the cause, are often perceived as responsible for their illness and less deserving of care.[3] Patients with chronic viral hepatitis experience stigma because they have an infectious illness that is viewed as associated with bad behaviour. Patients with alcoholic liver disease are viewed by some care providers as 'not only causally but also morally responsible for liver failure'[33] and undeserving of transplant. For example, patients with alcoholic liver disease are required to demonstrate 6 months of sobriety prior to consideration for transplant, even though many may die during this period and there is little evidence to support this practice.[34] The vast majority of patients with cirrhosis experience stigma and suffer deleterious consequences. A sensitive approach is required.

Case 26.1 (continued)

While awaiting transplant, G.B. experiences ongoing decline. His ascites is refractory to diuretics and he requires intermittent paracentesis. His concentration and sleep disturbances worsen despite lactulose and rifaximin therapy. He develops abdominal and diffuse pain, for which he receives low-dose acetaminophen, with poor effect. Over several days, his wife notices increasing confusion and weakness and G.B. is brought to the emergency department where he is diagnosed with acute renal insufficiency. He is treated with IV fluids, without improvement, and investigations confirm the diagnosis of hepatorenal syndrome. He is admitted to the ICU and treated with vasopressors, but renal function declines further, requiring dialysis. Palliative care is consulted to assist in the management of his delirium and worsening pain. Unfortunately, liver transplant is not possible and G.B. passes away in the ICU.

Question 7. What treatments are safe in the management of pain in ESLD?

Despite the high prevalence of pain in ESLD, there is little research into its causes.[2] The frequent and widespread pain of ESLD cannot be explained by ascites or SBP alone. One study hypothesized a relationship between fibromyalgia and the widespread pain of cirrhosis, but further research is needed.[35] The treatment of pain and other symptoms depends on understanding the effects of liver dysfunction on drug metabolism and following basic palliative care principles. The effects of many drugs are potentiated in ESLD, including opioids, benzodiazepines, NSAIDs, anti-epileptics, antibiotics, and antiemetics.[36] Acetaminophen, a known hepatotoxin in increased doses, is primarily excreted renally and may be used to treat pain in ESLD at a maximum dose of 2000 mg daily.[37] NSAIDs increase the risk of GI bleeding and can trigger hepatorenal syndrome and are not recommended. Cyclo-oxygenase 2 (COX-2) inhibitors have not been adequately studied.[37] Opioids can and are used, but caution is required to avoid sedation or HE. Most opioids have decreased clearance in ESLD, as both the cytochrome P450 system and glucuronidation are impaired.[37] Morphine and hydromorphone should be dose-reduced, and morphine metabolites present a greater risk of toxicity with renal insufficiency. The half-life of oxycodone is greatly prolonged in ESLD[36] and it should be used with great caution. Methadone does have significant hepatic metabolism; however, its use appears well tolerated. Fentanyl clearance is relatively unaltered and may be the safest choice in patients with ESLD.[36,37] Very little is known about the efficacy of various analgesic approaches in ESLD, and cautious initial drug doses should be chosen for the management of any symptom in ESLD, with the consideration for frequent consultation with a pharmacist.

Case 26.2

C.S. is a 62-year-old female presenting with severe abdominal pain, nausea, vomiting, and dehydration. She lives alone and has not worked for the last 5 years. Past history includes ongoing alcohol use and one pack per day (PPD) of cigarettes x 50 years. She had two prior admissions with acute pancreatitis, the last being 18 months ago requiring ICU admission. Physical exam reveals hypovolaemia and a tender abdomen without acute surgical findings. Computed tomography (CT) abdomen reveals evidence of acute-on-chronic pancreatitis without focal necrosis or fluid collection. She is treated with IV fluids and admitted to medicine for supportive care. C.S. clinically stabilizes but continues to have upper abdominal pain, radiating to her back and worst after eating. On further history, C.S. reports suffering from ongoing abdominal pain for several months but has not sought medical attention.

Question 8. What is the cause of C.S.'s persistent abdominal pain? How should it be treated?

C.S. has chronic pancreatitis, a debilitating condition associated with her recurrent episodes of acute pancreatitis. The prevalence of chronic pancreatitis is approximately 40/100 000 population.[38] Causes of chronic pancreatitis include alcohol and tobacco use, autoimmune pancreatitis, recurrent acute pancreatitis, and genetic susceptibility.[38] Pain often has a neuropathic component and is caused by multiple factors, including ductal obstruction and tissue inflammation.[39] Treatments include alcohol and tobacco cessation, uncoated pancreatic enzyme replacement with oral intake, proton pump inhibitors, NSAIDs, gabapentinoids, and opioids. A low-fat diet of frequent small meals may also be helpful. Experimental therapies include ketamine, clonidine, radiotherapy, and cannabinoids.[39]

Case 26.2 (continued)

C.S. is treated in hospital with small frequent meals, pancreatic enzyme replacement, pregabalin, and oral tramadol. Her pain improves, and she is discharged. She is able to abstain from alcohol and tobacco and manages in the community. She experiences a gradual decline, with diminished appetite, weight loss, and weakness, and eventually moves to long-term care. She is followed there by her general practitioner with special training in palliative care. Her opioid analgesia is titrated effectively and she passes away peacefully 6 months later.

Question 8. What other GI diseases are responsible for significant morbidity and mortality?

Causes of morbidity and mortality from non-cancer GI diseases include acute illnesses such as vascular disorders of the intestine, *Clostridium difficile* colitis, haemorrhage, and acute pancreatitis.[40] Crohn's and ulcerative colitis are truly chronic diseases, and management is best undertaken by a gastroenterologist in consultation with a pain specialist as required. In the unfortunate instance of patients developing a secondary cancer, this author suggests management be guided by the patient and their gastroenterologist. Other potentially fatal disorders include paralytic ileus, intestinal obstruction, and complications of diverticular disease.[40] Non-malignant intestinal obstruction is often surgically treated and non-surgical treatment would

generally involve a nasogastric tube for decompression and supportive care.[41] General palliative care principles apply to the management of all of the above, depending on the patient's goals of care.

Mesenteric ischaemia of the small bowel can cause significant morbidity and mortality.[40] It is classified as acute or chronic.[42] In acute ischaemia, usually due to an acute occlusive event, mortality is very high. These patients are treated aggressively with antibiotics, anticoagulation, and abdominal exploratory surgery. Pain is best treated with parenteral opioids. The prognosis of acute colonic ischaemia is less dire, and most patients survive with supportive care.[42] Chronic mesenteric ischaemia is associated primarily with severe atherosclerosis of the coeliac or superior mesenteric arteries, and many sufferers will die of other causes. Treatment involves disease-modifying therapies, including smoking cessation, medical management of atherosclerotic disease, and potentially angiographic treatment of vascular stenoses.[42] Pain is most often postprandial, often referred to as 'mesenteric angina', and is considered an indication for surgical or angiographic intervention.[42] Opioid therapy would be required if definitive therapies are not feasible or within the patient's goals of care.

Gastroparesis is a syndrome of impaired gastric emptying resulting in early satiety, nausea, vomiting, and bloating. Its causes include diabetes mellitus, post-surgery, neurological, mesenteric ischaemia, amyloidosis, and scleroderma,[43] and it may be seen as a complicating factor in patients receiving palliative care. Treatments include dietary modification, incorporating a 'small particle' diet, avoiding peels, seeds, fibre, and lipids, and small frequent meals.[43] If possible, minimize medications which delay gastric emptying, including opioids and anticholinergic agents. Pharmacologic treatments include metoclopramide and domperidone and would generally be preferred to other dopamine antagonists, as they have prokinetic properties.[43] IV erythromycin has also been used to treat gastroparesis; however, tachyphylaxis usually occurs.[43] Ondansetron and other $5HT_3$ antagonists may be added as an adjuvant. Emerging therapies include ghrelin receptor agonists (relamorelin) and agonists of the $5HT_4$ subclass of serotonin receptors (revexepride, velusetrag), but further research is needed.[43] In more severe instances, a venting gastrostomy could be considered.[43]

Summary

As the scope of palliative care expands and palliative strategies are incorporated earlier in the treatment of incurable diseases, it is essential that palliative care providers have the knowledge to care for patients with a wide variety of illnesses, importantly including those suffering from cirrhosis and other life-threatening GI diseases. These disorders highlight the importance of combining palliative care expertise with a detailed understanding of pathophysiology and active medical management. Research in palliative care for these illnesses is an emerging field.

References

1. **Angeli P**, **Bernardi M**, **Villanueva C** *et al.* (2018) EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*, **69**(2), 406–60. doi: 10.1016/j.jhep.2018.03.024
2. **Peng J**, **Hepgul1 N**, **Higginson IJ** *et al.* (2019) Symptom prevalence and quality of life of patients with end-stage liver disease: a systematic review and meta-analysis. *Palliat Med*, **33**(1), 24–36. doi: 10.1177/0269216318807051
3. **Vaughn-Sandler V**, **Sherman C**, **Aronsohn A** *et al.* (2014) Consequences of perceived stigma among patients with cirrhosis. *Dig Dis Sci*, **59**(3), 681–6. doi: 10.1007/s10620-013-2942-0

4. **Statistics Canada.** *Table 13-10-0394-01. Leading causes of death, total population, by age group*. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039401 doi: 10.1111/liv.13620.
5. **Murray CJ**, **Atkinson C**, **Bhalla K** *et al.* (2013) The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA*, **310**(6), 591–608. doi: 10.1001/jama. 2013.13805
6. **Langberg KM**, **Kapo JM**, **Taddei TH** (2018) Palliative care in decompensated cirrhosis: a review. *Liver Int*, **38**, 68–75.
7. **D'Amico G**, **Garcia-Tsao G**, **Pagliaro L** (2006) Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol*, **44**(1), 217–31.
8. **Salpeter SR**, **Luo EJ**, **Malter DS**, **Stuart B** (2012) Systematic review of noncancer presentations with a median survival of 6 months or less. *Am J Med*, **125**, 512.e1–6. doi: 10.1016/j.amjmed.2011.07.028
9. **Child CG**, **Turcotte JG** (1964) Surgery and portal hypertension. In: Child CG III (ed.) *The Liver and Portal Hypertension*, p. 50. WB Saunders, Philadelphia, PA.
10. **Pugh RN**, **Murray-Lyon IM**, **Dawson JL**, **Pietroni MC**, **Williams R** (1973) Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*, **60**(8), 646–9.
11. **Albers I**, **Hartmann H**, **Bircher J** *et al.* (1989) Superiority of the Child–Pugh classification to quantitative liver function tests for assessing prognosis of liver cirrhosis. *Scand J Gastroenterol*, **24**(3), 269.
12. **Gines P**, **Quintero E**, **Arroyo V** *et al.* (1987) Compensated cirrhosis: natural history and prognostic factors. *Hepatology*, **7**, 122–8.
13. **Les I**, **Doval E**, **Flavià M** *et al.* (2010) Quality of life in cirrhosis is related to potentially treatable factors. *Eur J Gastroenterol Hepatol*, **22**(2), 221–7. doi: 10.1097/MEG.0b013e3283319975
14. **Gordon F** (2012) Ascites. *Clin Liver Dis*, **16**(2), 285–99. doi: 10.1016/j.cld.2012.03.004
15. **Williams J**, **Simel D** (1992) Does this patient have ascites? *JAMA*, **267**(19), 2645–8.
16. **Rudralingam V**, **Footitt C**, **Layton B** (2017) Ascites matters. *Ultrasound*, **25**(2), 69–79. doi:10.1177/1742271X16680653
17. **Runyon BA** (2012) *Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. AASLD practice guideline.* https://www.aasld.org/sites/default/files/2019-06/AASLDPracticeGuidelineAsciteDuetoCirrhosisUpdate2012Edition4_.pdf
18. **Fukui H**, **Kawaratani H**, **Kaji K** *et al.* (2018) Management of refractory cirrhotic ascites: challenges and solutions. *Hepat Med*, **10**, 55–71
19. **Peabody CR**, **Mandavia D** (2017) Deep needle procedures: improving safety with ultrasound visualization. *J Patient Saf*, **13**(2), 103–8. doi: 10.1097/PTS.0000000000000110
20. **Macken L**, **Hashim A**, **Mason L**, **Verma S** (2019) Permanent indwelling peritoneal catheters for palliation of refractory ascites in end-stage liver disease: a systematic review. *Liver Int*, **39**(9), 1594–607. doi: 10.1111/liv.14162
21. **Valentina M**, **Lorenzo R**, **Jacob W** *et al.* (2008) The utility of the Model for End-Stage Liver Disease score: a reliable guide for liver transplant candidacy and, for select patients simultaneous hospice referral. *Liver Transpl*, **14**(8), 1100–6. doi: 10.1002/lt.21398
22. **Lamba S**, **Murphy P**, **McVicker S** *et al.* (2012) Changing end-of-life care practice for liver transplant service patients: structured palliative care intervention in the surgical intensive care unit. *J Pain Symptom Manag*, **44**(4), 508–19. doi: 10.1016/j.jpainsymman.2011.10.018
23. **Rush B**, **Walley KR**, **Celi LA** *et al.* (2017) Palliative care access for hospitalized patients with end-stage liver disease across the United States. *Hepatology*, **66**, 1585–91.
24. **Potosek J**, **Curry M**, **Buss M** *et al.* (2014) Integration of palliative care in end-stage liver disease and liver transplantation. *J Palliat Med*, **17**(11), 1271–7.
25. **Düll MM**, **Kremer AE** (2018) Management of chronic hepatic itch. *Dermatol Clin*, **36**(3), 293–300. doi: 10.1016/j.det.2018.02.008

26. **Hohl CM**, **Wong JK**, **Harlos MS** (2015) Methylnaltrexone to palliate pruritus in terminal hepatic disease. *J Palliat Care*, **31**(2), 124–6.
27. **Jones EA**, **Molenaar HA** (2007) Ondansetron and pruritus in chronic liver disease: a controlled study. *Hepatogastroenterology*, **54**(76), 1196–9.
28. **Merli M**, **Giusto M**, **Lucidi C** *et al*. (2013) Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. *Metab Brain Dis*, **28**(2), 281–4. doi: 10.1007/s11011-012-9365-z
29. **Vilstrup H**, **Amodio P**, **Bajaj J** *et al*. (2014) Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*, **60**(2), 715–35.
30. **Bajaj JS**, **Wade JB**, **Sanyal AJ** (2009) Spectrum of neurocognitive impairment in cirrhosis: implications for the assessment of hepatic encephalopathy. *Hepatology*, **50**(6), 2014–21. doi: 10.1002/hep.23216
31. **Acharya C**, **Bajaj JS** (2018) Current management of hepatic encephalopathy. *Am J Gastroenterol*, **113**(11), 1600–12. doi: 10.1038/s41395-018-0179-4
32. (2010) Stigma. In: *Oxford Dictionaries*. Oxford University Press, Oxford.
33. **Glannon W** (2012) Responsibility and priority in liver transplantation. In: Bayliss F, Borgerson K, Hoffmaster B, Sherwin S (eds.) *Health Care Ethics in Canada*, 3rd edn, p. 122. Nelson Education, Toronto, ON.
34. **Singhvi A**, **Welch AN**, **Levitsky J**, **Singhvi D**, **Gordon EJ** (2016) Ethical considerations of transplantation and living donation for patients with alcoholic liver diseases. *AMA J Ethics*, **18**(2), 163–73. doi: 10.1001/journalofethics.2016.18.2.sect1-1602
35. **Rogal SS**, **Bielefeldt K**, **Wasan AD**, **Szigethy E**, **Lotrich F**, **DiMartini AF** (2015) Fibromyalgia symptoms and cirrhosis. *Dig Dis Sci*, **60**(5), 1482–9. doi: 10.1007/s10620-014-3453-3
36. **Rhee C**, **Broadbent AM** (2007) Palliation and liver failure: palliative medications dosage guidelines. *J Palliat Med*, **10**(3), 677–85.
37. **Chandok N**, **Watt KD** (2010) Pain management in the cirrhotic patient: the clinical challenge. *Mayo Clin Proc*, **85**(5), 451–8. doi: 10.4065/mcp.2009.0534
38. **Park W** (2016) Clinical chronic pancreatitis. *Curr Opin Gastroenterol*, **32**(5), 415–21. doi: 10.1097/MOG.0000000000000293
39. **Kleeff J**, **Whitcomb DC**, **Shimosegawa T** *et al*. (2017) Chronic pancreatitis. *Nat Rev Dis Primers*, **3**, 17060. doi: 10.1038/nrdp.2017.60
40. **Peery A**, **Crockett S**, **Barritt A** *et al*. (2015) Burden of gastrointestinal, liver, and pancreatic diseases in the United States. *Gastroenterology*, **149**(7), 1731–41.e3. doi: 10.1053/j.gastro.2015.08.045
41. **Hajibandeh S**, **Hajibandeh S**, **Panda N** *et al*. (2017) Operative versus non-operative management of adhesive small bowel obstruction: a systematic review and meta-analysis. *Int J Surg*, **45**, 58–66. doi: 10.1016/j.ijsu.2017.07.073
42. **Kolkman J**, **Geelkeren RH**, Diagnosis and treatment of chronic mesenteric ischemia: an update. *Best Pract Res Clin Gastroenterol*, **31**(1), 49–57. doi: 10.1016/j.bpg.2017.01.003
43. **Stein B**, **Everhart K**, **Lacy BE** (2015) Gastroparesis. A review of current diagnosis and treatment options. *J Clin Gastroenterol*, **49**(7), 550–8. doi: 10.1097/MCG.0000000000000320

Chapter 27

Palliative care in the community

Anne B. Boyle and David Henderson

Attitude

To enable each learner to:

- Reflect on the importance of initiating a palliative approach to care early in a disease trajectory.
- Reflect on the importance of providing palliative care to people in their own, communities, and homes.
- Reflect on the importance of a multidisciplinary approach to palliative care.
- Reflect on the importance of primary care on the delivery of palliative care in the community.

Skills

To enable each learner to:

- Integrate the essential features of the history and natural disease trajectory in identifying people who would benefit from a palliative approach to care.
- Systematically assess the needs of patients in the community.
- Help the patient plan by discussing advance care planning, having goals of care discussions, and developing treatment plans.
- Link the patient to appropriate resources in their community.
- Plan for emergencies.

Knowledge

To enable each learner to:

- Formulate a treatment plan to manage physical symptoms and psychosocial and spiritual needs.
- Recognize some of the essential conversations that are usually required and how to do a family meeting.
- Recognize when it may be appropriate to refer to a specialist palliative care team for additional support.

Case 27.1

Dr B.H. arrives at her office on Monday morning and begins telling her colleagues about the great LEAP (Learning Essential Approaches to Palliative Care)[1] course she attended this past weekend. She has always been interested in caring for people throughout the trajectory of their illnesses, including to the end of life.

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Having completed her family medicine residency 3 years ago, she still feels less confident in her ability to deliver primary palliative care than she wants to. The LEAP course, taught by two certified instructors from her local specialist palliative care team, provided her with a good review of many of her skills and helped to solidify her understanding of areas where she was less comfortable. It also provided her with an opportunity to get to know other healthcare professionals from her region with a common interest. She got to meet one of the palliative care physicians Dr P.C., the public health nurse (PCRN) H.H., and the palliative care social worker C.A. Their team provides education to healthcare professionals and healthcare students and consults and/or shared care for challenging cases, and participates in research to advance palliative care in Canada. Being in a small area with a population of about 80 000 people, the specialty team consists of two palliative care consultant physicians, six community-based PCRNs, and a community-based palliative care social worker.[2] The team also has a volunteer coordinator who recruits, trains, and manages over 50 palliative care volunteers. They see people in their homes, in hospital, or in other care settings. They have access to a few excellent spiritual care providers from the area who are willing to see someone at the recommendation of the team.

One of her first patients of the day is J.B., a 55-year-old steel worker. He has never been married. He lives alone in a 2-storey walk-up. He is a 40-pack year smoker. He has been hospitalized three times in the past 6 months due to shortness of breath. He has no plans to deal with dyspnoea exacerbations at home. He is losing weight and has become increasingly weak. He was recently readmitted, and computed tomography (CT) shows there is no cancer, but severe worsening fibrotic lung disease. J.B. does not want to be considered for transplant, despite the insistence of his respirologist, as he really does not like doctors or hospitals. Remembering her LEAP training, Dr B.H. thinks J.B. may be appropriate for a 'palliative approach to care'.

Question 1. What is the palliative approach to care?

A palliative approach to care is applying the philosophy of palliative care earlier on in the trajectory of an illness to help improve the person's quality of life. It involves basic symptom management, advance care planning, and goals of care, and ensuring adequate supports for care are in place based on needs.[3]

Question 2. When do you know it is time to apply the palliative approach? What is included in it?

Case 27.1 (continued)

Dr B.H. starts by asking herself, 'Would I be surprised if J.B. died in the next year?'. Reviewing his diagnosis of advanced pulmonary fibrosis, functional decline, frequent exacerbations, and weight loss, she feels strongly he would benefit from a palliative approach. She begins by thinking through this approach systematically:

1. *What is included in a palliative approach?*
   a. *Identify*—identify people early who may benefit from palliative care.
   b. *Assess*:
      i. Their understanding of their condition and information needs.
      ii. Symptoms.
      iii. Psychosocial and spiritual needs.
      iv. Quality of life.
      v. Values, wishes, and preferences.

c. *Plan*:
   i. Advance care planning.
   ii. Goals of care and care plans.
   iii. Treatment plans.
   iv. Link to resources and other care providers.
   v. Prepare for emergencies.
d. *Manage*:
   i. Symptoms.
   ii. Psychosocial and spiritual needs.
   iii. Essential discussions.
   iv. Refer for assistance as needed.

Question 3. How do we begin to apply the palliative approach?

Case 27.1 (continued)

Dr B.H. starts with reviewing J.B.'s recent history and asks him his thoughts on how this is unfolding. She reviews the discussions he has had with his respirologist and the choices he has made to not pursue aggressive treatments.

She offers to speak with him more about this but, for today, wants to review his symptoms and see if she can help him to be more comfortable. She provides him with an Edmonton Symptom Assessment Scale (ESAS)[4] and asks him to record how he feels right now. He reports:

Pain—4/10.
Tiredness—6/10.
Drowsiness—4/10.
Nausea—0/10.
Appetite—5/10.
Shortness of breath—6/10 at rest; 9/10 with walking 10 m.
Depression—2/10.
Anxiety—4/10.
Best well-being—4/10.

When asked about his greatest fears, he quickly states, 'I'm afraid I will suffocate to death'. Dr B.H. begins with explaining some of the options for managing dyspnoea. Her history and physical exam reveal that he has had 3 days of increased cough and wheeze with green sputum production. He has been using his 'blue' puffer much more often. His chest reveals consistent fibrotic crackles at both bases. At this time, Dr B.H. opts to treat him with a 5-day course of prednisone 50 mg each morning and doxycycline 100 mg po twice a day for 10 days. As well, for his dyspnoea, which has been quite consistent for the last few months, she suggests a trial of low-dose morphine. He is initially nervous when he hears the word morphine. She asks him if he remembers ever taking Tylenol #3™ which has 30 mg of codeine. He said he did in the past, with no side-effects. She explains to him that codeine is broken down in the liver into morphine at a 10:1 ratio. This means taking one Tylenol #3™ (30 mg of codeine) = taking 3 mg of morphine. She suggests starting him on a low dose of morphine 2.5 mg po four times a day. The explanation helps ease his mind. She starts him on some polyethylene glycol as a laxative to prevent constipation and provides metoclopramide to use if nausea develops. With all these changes, she asks him to return in 3 days for follow-up or to call sooner if he loses any ground.

Question 4. What are some of the challenges faced in managing symptoms in the community?

- Do you have access to the medications required?
- Does the patient have the ability to pay for the medications and supplies required?
- Does the patient have transportation to come in for follow-up?
- Is the patient able to clearly follow recommendations?
- Is there a home care system in your area that can help with care and follow-up?

Case 27.1 (continued)

Dr B.H. has trained her office staff to pay particular attention to her list of patients she has initiated a palliative approach on, as she recognizes they can change quickly and may need rapid interventions. This includes having the staff put calls through to her from home care nurses phoning about patients on this list.

At the next visit, Dr B.H. plans to delve more into the palliative approach with J.B., focusing on advance care planning, developing a rescue plan for exacerbations, and exploring psychosocial issues, and will consider linking him with additional resources. She now feels confident that if she has any questions, she can call her colleagues on the specialist palliative care service for advice, support, or a referral if needed.

Case 27.2

Halfway through Monday morning, Dr B.H. meets a new patient she agreed to take on. F.F. is a 69-year-old female who lives alone on her 100-acre family farm. She had three children—one died at age 28 of an opioid overdose, and one died recently at age 52 of a myocardial infarction (MI). Her daughter is very supportive and lives in another province with her family. F.F. was in good health and still actively involved in her local and church community until recently when she began to feel more tired and weak. Her appetite decreased and she lost 12 pounds unexpectedly. Unfortunately, her long-time family doctor retired 10 months ago and they have not been able to find a replacement.

She went to the local emergency department (ED) when she began vomiting. She was sent to a regional teaching centre and a CT scan showed a bowel obstruction with metastatic disease to the liver/lung. She chose to have a diverting colostomy. Post-operatively, the surgeon wanted to send her back to her local hospital for recovery, but there was no admitting physician. F.F. wants to be with her daughter but cannot travel with how weak and ill she is, and she is concerned about health coverage. Her first choice is to go to her home. She would like 'to see the farm at least one last time'.

Question 5. What factors affect delivery of palliative care in the community?

Access to primary care is an issue in some communities. This can lead to decreased preventative medicine and screening, delay in investigation of symptoms, and lack of access to optimal place of care for end of life. There are rarely hospice options in small rural communities.

Case 27.2 (continued)

F.F. and her family are thrilled Dr B.H. has agreed to take on her care. F.F.'s daughter chooses to take a leave from her work to support her mother.

Question 6. What resources exist to help support patients in the community?

Case 27.2 (continued)

Her daughter, with the support of her family doctor, accessed Compassionate Care Benefits (https://www.canada.ca/en/services/benefits/ei.html).[5]

The teaching hospital provided prescriptions for 2 months of medication for the patient and her daughter on discharge.

The church community and neighbours were there to help support the patient and her daughter. F.F.'s daughter accessed the Canadian Virtual Hospice (CVH) website[6] to learn how to give a bed bath and was able to access caregiver support through the online section 'Ask a Professional'. Unfortunately, after 3 weeks, the patient's symptoms of dyspnoea and delirium worsened acutely. The daughter did not know what to do. Despite her mother's protests, she was taken to the local ED. The ED doctor (a colleague of Dr B.H.) treated the symptoms and referred F.F. to Dr B.H. for primary care supports.

Fresh off her LEAP course, Dr B.H. recognized that F.F.'s rate of decline was rapid, with her Palliative Performance Scale (PPS)[7] dropping from 60% (reduced ambulation; unable to do hobby/housework; significant disease; occasional assistance necessary) to 40% (mainly in bed; unable to do most activity; extensive disease; assistance mainly needed) over the last 4 weeks.

Case 27.2 (continued)

Her ESAS score[4] showed F.F.'s pain at 5/10 and nausea at 6/10, but dyspnoea now at 5/10. She remains slightly delirious. The severity of her mother's symptoms has distressed the daughter and she is worried that she may not be able to care for her mother at home despite her mother's wishes.

Question 7. What steps need to be taken to optimize the ability of the patient to be cared for in the community?

Case 27.2 (continued)

Dr B.H. recognizes the complexity of the situation and discusses a referral to the specialist palliative care team for some additional support. F.F. and her family agree. In the meantime, Dr B.H. starts working on managing F.F.'s symptoms, focusing first on her pain and nausea. Her mild delirium clears with some hydration. Dr B.H. has already introduced the concept of advance care planning, as F.F. and her family had not begun those conversations despite F.F. having some clear ideas of what she did and did not want.

A couple of days later, Dr B.H. got a call from H.H., the PCRN. They briefly reviewed the case by telephone and H.H. set up a time to meet with F.F. and her family, along with the palliative care social worker. Upon meeting, they helped to put the patient and her family's minds at ease by helping them understand that accessing palliative care does not mean you have to be in your last few weeks or days of life. 'This is a needs-based programme here to help support you, your family, and your primary care team.'

A thorough review of F.F.'s history and assessment of her current symptoms revealed that her nausea was much improved with the scheduled antiemetic regimen. Her nausea was improved now, being down from 6/10 to 1/10 on her repeat ESAS. She had not started the low-dose morphine that was recommended in the ED for her dyspnoea which was still a problem at 5–6/10. With further exploration, it

was discovered that she was frightened by the thought of starting an opioid because of her son's death from overdose. A thoughtful discussion took place with F.F. and her daughter to help them understand dyspnoea and the treatment options available to her. She agrees to try very low-dose morphine by mouth at 1 mg every 4 hours and 1 mg every 1 hour as required. She recognizes the benefit and works with her team to get her symptoms better controlled. Her dyspnoea and pain responded to the morphine. She has now been titrated up to morphine 5 mg po q4h and 2.5 mg q1h PRN for breakthrough, of which she only needs 1–2/day. Upon review, her bowels were not working well, so the addition of Senokot™ on a regular basis was also recommended. H.H. also contacted Dr B.H. and suggested that they could now look at switching F.F. over to a long-acting morphine to improve compliance and simplify her medication regime.

Dr B.H. had also arranged for home care nursing to start in order to help monitor F.F.'s symptoms, as it was getting harder for her to come to her office. They discussed alternate places for care in case home becomes too difficult. Volunteers and the local church community create a schedule to support the daughter, as F.F. is now a two-person assist to get up. They also provide support for meals and cleaning.

F.F. and her family went on to use the website https://www.advancecareplanning.ca [8] and used their provincial workbook to help facilitate a good discussion for an advance care plan. Her daughter even realized it would be good for her to start to consider this for herself.

Dr B.H. stayed in touch with F.F. through contact with H.H. (PCRN) and subsequently did a couple of joint home visits with him over the next 3 weeks. Over the last few days, F.F. has gotten much weaker. Her goals of care are clear in that she wishes to stay at home and forgo any further testing.

Dr B.H. does a final home visit with H.H. to see F.F. and her family. They quickly review her goals of care and sit with them to review and plan for the days ahead. A medication review is completed and some medications are now deprescribed as their value at end of life is negligible. The necessary ongoing medications are switched to subcutaneous administration, as F.F. is beginning to have difficulty swallowing. This includes her opioid for pain and dyspnoea, and haloperidol to help with nausea and delirium should it arise. Orders are prepared for her home care nurse to insert the subcutaneous lines, preload medications, and instruct the family on how to administer the medications.

A calendar outlining the medications (using both names) and their purposes, dosages, and administration times is produced and reviewed with the family to ensure their understanding. Safe disposal of unused medications is discussed with the family and F.F.'s daughter is identified as the person who would return the medications to their pharmacy. The palliative care social worker is following up with F.F.'s daughter and provides information to her about grief for her and her family, as well as navigating some of the practical needs of banking, Canada Pension Plan issues, and accessing some private care to help with respite. Home care nurses are scheduled for daily visits and the PCRN checks in periodically with the home care nurses, F.F., and her family. Information is provided about the last days and hours of life verbally and in written form for the family to be able to review. F.F. dies very comfortably a few days later in her own home, as she had wished. After F.F.'s death, Dr B.H. dropped in to check on how her daughter was doing and ask if she has any questions. F.F.'s daughter was appropriately sad, but grateful for the wonderful care they received from the whole team, including the volunteers who had visited, the home care team, the palliative care nurse, and the social worker, and especially Dr B.H. for her kindness and compassion.

Question 8. What is interprofessional care?

They say it takes a village to raise a child. That same village should be there at the end of our life as well. Communication is key. The complex health needs of patients who die at home require a team approach to address patient and family needs by providing integrated compassionate care. The Canadian Interprofessional Health Collaborative (CIHC)[9] has published six competency domains necessary for interprofessional collaborative practice (see Box 27.1).

Box 27.1 The CICH six competency domains

- Role clarification
- Team functioning
- Patient/family/community-centred care
- Collaborative leadership
- Interprofessional communication
- Interprofessional conflict resolution

Adapted with permission from Canadian Interprofessional Health Collaborative. (2010) A National Interprofessional Competency Framework. Available from http://www.cihc-cpis.com/publications1.html

Care providers, caregivers, and patients must exchange knowledge and expertise and integrate what is learnt with, from, and about each other to deliver the common goal of optimal patient care.

References

1. **Pallium Canada**. https://www.pallium.ca
2. **Henderson JD**, **Boyle A**, **Herx L** *et al.* (2019) Staffing a specialist palliative care service, a team-based approach: expert consensus white paper. *J Palliat Med*, **22**(11), 1318–23. https://doi.org/10.1089/jpm.2019.0314
3. **Canadian Hospice Palliative Care Association** (2014) *The Way Forward National Framework: a roadmap for an integrated palliative approach to care. The Way Forward Integration Initiative.* www.hpcintegration.ca/media/54625/TWF-framework-doc-Eng-2014-final.pdf
4. **Hui D**, **Bruera E** (2017) The Edmonton Symptom Assessment System 25 years later: past, present and future developments. *J Pain Symptom Manage*, **53**(3), 630–43.
5. **Government of Canada**. *Employment Insurance benefits and leave*. https://www.canada.ca/en/services/benefits/ei.html
6. **Canadian Virtual Hospice.** https://www.virtualhospice.ca
7. **Palliative Performance Scale** (PPSv2) version 2, Victoria Hospice Society. Available from https://victoriahospice.org/how-we-can-help/clinical-tools/
8. **Advance Care Planning Canada.** *Advance Care Planning in Canada*. https://www.advancecareplanning.ca
9. **Canadian Interprofessional Health Collaborative** (2010) *A National Interprofessional Competency Framework*. http://www.cihc.ca/resources/publications

Chapter 28

Palliative care in the intensive care unit

Valerie N. Schulz and James Downar

Attitude

To enable each learner to:

- Balance intensive care unit (ICU) priorities with palliative care priorities.
- Appreciate the challenges involved in prognostication and view critical illness in the context of the overall trajectory of illness.
- Have an approach to ethical challenges that arise in the seriously ill.

Skills

To enable each learner to:

- Apply a palliative approach to care within the ICU setting.
- Demonstrate methods of communication and collaboration with the patient, substitute decision-makers (SDMs), and ICU interprofessional team.

Knowledge

To enable each learner to:

- Cite the common symptoms experienced by critically ill patients.
- Describe different models of integrating palliative care in the ICU.
- List common triggers that help ICU teams to identify patients who may benefit from a palliative care consultation/palliative approach to care.
- Know the current guidelines for managing pain, agitation, delirium, and sleep disturbance in the ICU setting.
- Identify future considerations for palliative discussions and decision-making in the ICU.

Introduction

Why would palliative principles of care be needed for patients in the ICU? Given our ageing population and advancements in healthcare, people live longer with chronic illnesses which can decline into critical illness with relatively minor health challenges. When these patients have a sudden decline, they are often not prepared to consider a palliative approach to care. They request acute care, including ICU, hoping to recover. The ICU is designed for patients with acute, potentially reversible illness, so when patients with complex chronic illness and uncertain prognosis are admitted to the ICU, this can create challenges for communication and decision-making.

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Case 28.1

T.R. is 83 years old with progressive frailty and multi-morbidity, including diabetes, vascular disease, chronic obstructive pulmonary disease (COPD), and chronic kidney disease. She has required assistance with activities of daily living for 6 months and receives oxygen at home by nasal cannulae. She has two supportive daughters. Her husband died 3 years ago. She was admitted to hospital today with community-acquired pneumonia and has requested full resuscitation in the event of deterioration. Twelve hours post-hospital admission, T.R. requires ICU admission for management of respiratory failure and sepsis.

Question 1. Are patients with chronic or progressive life-limiting illness admitted to the ICU?

The proportion of patients who die in the ICU varies by country.1 However, one in five Americans dies in, or shortly after, an ICU stay.[2] People with chronic illness admitted to the ICU often receive invasive interventions to prolong life, but their symptomatic, psychosocial, and spiritual needs can be left unmet. This is unfortunate, because a palliative approach to care can be well supported in the ICU setting.[3]

Question 2. Can ICU physicians predict mortality with certainty?

Tools to help predict ICU mortality are based on average risks, rather than on certainty, for an individual patient. Examples include: the Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE II/III), and Simplified Acute Physiology Score (SAPS) II.[4] Although people with treatment-refractory metastatic cancer (especially with metastases to the lung) tend to have high mortality in the ICU, the severity of organ failure, performance status, and the use of mechanical ventilation predict mortality better than their cancer characteristics.[5] The risk of dying may be unclear for some patients and many ICU clinicians will admit patients for a 'time-limited trial' of ICU therapy;[6] a reasonable duration would range between 3 and 7 days. The patient's response to treatment during this trial can be helpful in prognostication.[7]

Question 3. Does pre-existing illness affect ICU outcomes?

The patient's pre-existing functional, cognitive, and psychosocial status affects ICU outcomes and should be considered in treatment decision-making.[7] The patient's functional trajectory is an important part of a comprehensive assessment, and it can help frame the goals and plan of care.[8] Traditional palliative care was rooted in the care of patients with cancer, who typically deteriorate in a predictable, unidirectional, relentless, and accelerating manner. In contrast, patients dying of chronic organ failure often experience sudden, unpredictable episodes of acute-on-chronic organ failure, which can allow little time for communication and palliative transition before ICU admission is considered.[10,11]

Case 28.1 (continued)

On arrival in the ICU, T.R. requires intubation, ventilation, vasopressors, and, 2 days later, haemodialysis. She is diagnosed with delirium and is unable to participate in conversations. The ICU team meets with her daughters who are joint SDMs, to inform them that T.R.'s survival is uncertain. Her daughters state that T.R. told

them that if she should ever become ill, she would want aggressive treatment if there was some hope for survival and quality of life after treatment. They agree she would want to continue treatment for her pneumonia. The ICU team wonders if a palliative care consult is appropriate.

Question 4. Can the ICU 'rescue' culture and the palliative approach to care coexist?

The ICU environment features technology, noise, invasive monitoring, and often little privacy. This is different from the environment of a palliative care unit. However, ICU and palliative care providers have advocated for the integration of a palliative approach to care within the ICU environment,[9,10] and researchers have studied palliative interventions in ICU settings.[11,12] The core elements of palliative care[13] (e.g. symptom management, communication about goals of care, and family support) are highly relevant in the ICU, and palliative interventions do not compromise survival.

Question 5. How can palliative care be integrated within the ICU?

Models of integrating palliative care in the ICU can range from an integrative model to a purely consultative model, or a mix of the two.[14,21] In the integrative model, ICU staff are educated in palliative care practices as core components of intensive care, and other resources and quality assurance processes are established within normal ICU workflow.[18] This model permits a palliative approach to care for all patients and reduces the demand on the consultant palliative care service. However, this model requires maintenance of competence for ICU providers and depends on a committed ICU culture, administration, resources, and staff.

The consultative model involves palliative care teams providing consultation in the ICU setting for selected patients, including those with complex needs.[14] The provision of care is determined by the level of ICU expertise and the availability of palliative care teams. The palliative team can offer continuity of care for patients who are subsequently transferred to a ward, or a palliative care unit or hospice.

Question 6. When does an ICU team consult palliative care?

Referral patterns vary by ICU, according to the culture of the unit, the attitude of individual ICU physicians towards palliative care, and palliative care team availability. Some ICU teams use 'triggers' and findings from routine assessments (undertaken on admission and daily) to prompt a palliative care consult[15] (see Table 28.1). Some ICU teams invite a palliative care team member to attend ICU rounds to identify appropriate patients for a palliative care consult.[16]

Case 28.1 (continued)

Two weeks later, T.R. is recovering from her pneumonia and delirium, but she remains dependent on mechanical ventilation and haemodialysis. She communicates through mouthing words and hand signals. She demonstrates distress through facial grimacing. The ICU team consults palliative care to collaborate on symptom management and decision-making. Her assessment reveals that she has abdominal pain, breathlessness with ventilator weaning, and thirst, and requires two people to assist her when transferring from bed to chair. The palliative care team suggests a patient and family conference to discuss goals of care.

Table 28.1 'Triggers' to aid in when to request a palliative care consult in the ICU

Triggers	Characteristics
Baseline patient characteristics	Provider would not be surprised if they died in the next year or before adulthood Decline in function/feeding Significant unintentional weight loss Admission from long-term care Previously identified palliative/hospice patient No previous advance care plan Weak social support network Patient/family request for palliative care
Selected acute diagnoses	Elderly, cognitively impaired patient with hip fracture Out-of-hospital oxygen use or cardiac arrest Incurable cancer
Additional healthcare use criteria to be assessed daily during hospital admission	Difficult-to-control physical/psychological symptoms >24/48 hours Tracheostomy or gastrojejunostomy placement ICU admission >7 days Recurrent ICU needs in same admission Lacking clear goals of care Limits placed on life extension interventions ICU physicians' concern for poor patient outcome, e.g. prolonged multi-organ failure Potential palliative care unit/hospice transfer Differences/distress in setting collaborative team/patient/SDM goals and plans of care

Source: data from Weissman DE, Meier DE. 'Identifying Patients in Need of a Palliative Care Assessment in the Hospital Setting. A Consensus Report from the Center to Advance Palliative Care', *Journal of Palliative Medicine*, Vol. 14, Issue 1, pp.1–7. (2011) Mary Ann Liebert, Inc.

Question 7. What palliative interventions are important to patients and their SDM?

Symptom assessment and management are core features of the palliative approach to care (see Table 28.2). According to patients and SDMs, communication, patient-focused decision-making, maintaining patient comfort and respect, and caring for the family are essential components that define high-quality palliative care in the ICU (see Table 28.3).[17]

Question 8. What symptoms are commonly experienced by ICU patients?

ICU patients commonly experience pain, dyspnoea, anxiety, restlessness, agitation, delirium, thirst/dry mouth, sleep disturbances,[11,18] and numbness and weakness from critical illness polyneuromyopathy[19] (see Table 28.2 for management considerations).

Consensus guidelines for the management of ICU-related pain, agitation, delirium, and sleep disturbances[20] recommend a protocol-driven, stepwise approach for analgesia, including non-pharmacological approaches. Analgesia and sedation are often required, especially early in an ICU stay, for the patient to tolerate life-sustaining ICU interventions. The guidelines recommend an analgesia-first approach before giving sedatives for agitation and, if possible, light sedation

Table 28.2 ICU patient symptom characteristics and management considerations

Symptom	ICU-related symptom issues	Management considerations[28]
Pain	Diagnostic/treatment-related procedural pain, for example: central and peripheral venous/arterial cannulae, chest tubes, oral tracheal tubes, tracheostomy, tracheal suction, mechanical ventilation, nasogastric tube insertion, and *in situ* ear and pharyngeal pain, restraints, urinary catheter, stool collection systems, turning, or wound care and drains	Consider: the intention of the intervention; pain assessments for communicating and non-communicative patients ex. critical care pain observation tool, analgesic needs, considering age, level of consciousness and patient wishes, prior opioid use, organ dysfunction, pre-emptive analgesia, etc.
Dyspnoea	Respiratory failure is a common reason for ICU admission. Moderate to severe dyspnoea is present in 34–60% of ICU patients. Causes: resistance to ventilation, respiratory muscle weakness, pulmonary infections, adult respiratory distress syndrome, asthma, obstructive lung, and cardiac disease. Patient expression of dyspnoea can be anxiety, fear, restlessness, agitation, dyssynchrony with ventilation, sweating, and accessory muscle use	Review effectiveness of ventilation, potential opioid use, disease-specific treatments (e.g. corticosteroids, antibiotics when indicated)
Anxiety	Subjective experience of apprehension with feelings of uncertainty; 53–63% of ICU patients report nervousness, irritability, nausea, dry mouth, insomnia, or trembling. May be associated with a new environment, communication limitations, uncertain prognosis, pain, dyspnoea, sepsis, heart or lung disease, or medication use or withdrawal	Treat the underlying cause (e.g. pain, dyspnoea, fear) Provide psychological support
Restlessness Agitation	The inability to relax, fidgeting, being in constant motion, combative to aggressive behaviour that is harmful to self and others Monitor with the Sedation-Agitation-Scale, Richmond Agitation Sedation Scale, or other similar available scales	Assess and treat specific causes of restlessness and agitation Assess for alcohol withdrawal and delirium
Delirium	An acute brain dysfunction with deficits in orientation, memory, and executive functions. Associated with increased length of ventilation, stay, and mortality, and may be associated with reduction in functional status and cognition in ICU survivors. Two validated ICU delirium assessment tools: Intensive Care Delirium Screening Checklist (ICDSC) and the Confusion Assessment Method for the ICU (CAM-ICU)[35]	Consider and address likely causes of delirium Avoid antipsychotic medications for prevention or treatment of hypoactive delirium Use dexmedetomidine for agitated delirium Monitor for adverse effects if neuroleptics are trialled

(*continued*)

Table 28.2 Continued

Symptom	ICU-related symptom issues	Management considerations[28]
Sleep disturbances	Sleep occurs in four stages of non-rapid eye movement (REM) and REM sleep. Disturbances of sleep occur in 42–68% of ICU patients, but not clearly understood. Some of these include: delayed onset, fragmented sleep, and change in sleep stages Sleep disturbance may be caused by underlying illness and the environment, including light and noise, as well as by monitoring invasively. Mechanical ventilation, pain, delirium, or medications are other contributors. These are felt to be associated with changes in psychological function, lower quality of life, and morbidity	Reduce noise and light at night No specific pharmacologic therapy is recommended
Thirst/dry mouth	Occurs in 40–78% of patients. Causes: low body fluids, increased osmolarity, mouth breathing, infections, medications (anticholinergics, diuretics, opioids, corticosteroids), vomiting, diarrhoea, fever, or blood loss. Monitor via self-assessment and physical exam	Mouth care, oral cleansing agents, ice chips Artificial saliva, saliva substitutes
Acquired weakness: critical illness, polyneuropathy or myopathy[27]	Common significant cause of weakness, increased length of ICU stay, delayed weaning from ventilation, and rehabilitation. Involves axonal degeneration of peripheral motor and sensory nerve fibres, sparing autonomic and cranial nerves Type II fibres atrophy, weakening the diaphragm and intercostal muscles Risk factors: sepsis, systemic inflammatory response syndrome, or multi-organ dysfunction	Treat underlying risk factors and consider physiotherapy or rehabilitation programme Weakness resolves in weeks to months, although patients may have permanent residual weakness

only. For delirium, the guidelines recommend avoiding antipsychotics for prevention or treatment of hypoactive delirium, and using only dexmedetomidine for treatment of agitated delirium. For sleep disturbance, guidelines recommend noise and light reduction, but no specific pharmacological therapy.

Table 28.3 Domains of high-quality palliative care in the ICU from the patient and SDM perspective

Domains	Characteristics
Communication	Timely, clear, and compassionate about the patient's illness, treatment, and prognosis
Patient-focused decision-making	Identifying the patient's preferences, goals, and values
Maintaining patient	Comfort, dignity, personhood, and privacy
Caring for the family	Interprofessional support Access to the patient Bereavement support if the patient dies

Source: data from Nelson JE, et al. 'In their own words: Patients and families define high-quality palliative care in the intensive care unit', *Clinical Investigations*, Vol. 38, Issue 3, pp.808–18. (2010) Wolters Kluwer Health Inc.

Question 9. What circumstances influence symptom management in the ICU?

Palliative providers should collaborate with ICU providers and become aware of site-specific ICU sedation, analgesia, pain, agitation, and delirium assessment tools and protocols. Based on the goals of care, the team may select different symptom management targets.

Consider the patient's tolerance of intravenous or arterial cannulae, drainage tubes or catheters, artificial airways, wound dressings, monitors, etc., while titrating medications to facilitate patient care.21 There are validated tools to assess consciousness, agitation, motor activity, sleep, pain, and patient–ventilator synchrony, and these assessment tools can be useful to achieve both palliative and curative goals.

There may be situations where deeper sedation is required to achieve symptom control. Symptoms that are refractory to usual therapies (e.g. pain refractory to non-pharmacological interventions, analgesics, adjuvants, and interventional techniques) for a patient in their last hours to days of life may require palliative sedation (see Chapter 20).

Question 10. How can conscious, non-verbal ventilated patients communicate?

Day-to-day communication with conscious, ventilated ICU patients is essential. New sedation and pain management guidelines have resulted in more awake, ventilated patients. Effective communication can reduce patient distress and aid symptom management,22 so palliative and ICU teams could consider a unit-wide strategy around effective communication methods.

An algorithm describing methods of communication for ventilator-dependent patients has been described.23 This algorithm guides assessment of consciousness, cognition, hearing, and visual and functional abilities, then tailors communication strategy based on fine motor abilities. Can they write or use a letter board or computer? Do they have a tracheostomy? Can speaking valves or an electrolarynx be used when appropriate?.

Question 11. What are ICU communication, decision-making, and family support strategies?

Communication and decision-making are challenging in the ICU. Responsibility for decision-making shifts to SDMs when patients are unable to make decisions for themselves. There are numerous tools to assist with shared decision-making.24 Printed materials for patients and families, palliative or ethics consults, and structured ICU team communication reduce family distress, improve comprehension, reduce the number of intensive treatments, and decrease the length of ICU stay.33

Patient values and preferences are central components of communication and decision-making. Providers need to develop skills to elicit and incorporate patient values and preferences into decision-making conversations.25 At times, these conversations can evoke strong emotional responses; providers need to be skilled at handling these responses, diffusing tension, and de-escalating conflict. Providers can facilitate this process by being receptive, identifying supports for the patient or SDM, and recognizing the different roles that SDMs may wish to play in these conversations.

Case 28.1 (continued)

At the family meeting, T.R. describes her symptoms as tolerable, but she appears to have a poor understanding of her current situation. T.R.'s advance care plan indicates she would not want to be dependent on 'machines'. The care team believes that she is likely to require mechanical ventilatory support and haemodialysis for the foreseeable future, given her poor recovery to date. Her daughters are not ready to consider withdrawal of mechanical ventilatory support, as T.R. is awake and recognizes them. They wonder if T.R. considered this circumstance when she developed her advance care plan. Her daughters request an extended ICU stay, hoping that she can wean from ventilation and her kidneys recover. They understand that their mother is frail and at risk of dying, and they agree to withholding cardiopulmonary resuscitation should T.R. suffer a cardiac arrest.

Question 12. How do ICU decision-making and patient death affect the family?

Psychological distress complicates decision-making, but it can be challenging to reduce distress among SDMs. One study of a dedicated intervention of daily communication and emotional support for SDMs of patients admitted to the ICU found that while the SDMs appreciated the improved communication with clinicians, the intervention did not reduce psychological distress in the SDMs and their symptoms of anxiety, depression, and post-traumatic stress remained high for 6 months after the ICU admission.26 Discordance between the physician's and the SDM's perceptions of ICU prognosis can also be common and frustrating,27 and it can be difficult to resolve this discordance or reduce the distress it causes.28 There are ongoing studies of techniques to reduce SDM distress and improve communication and decision-making support.29

Complicated grief is seen in as many as 52% of adults who experience the death of a family member in the ICU—a prevalence that is up to fivefold higher than the general population. Complicated grief is serious, as it can result in the development or worsening of physical or mental health problems. Complicated grief is more common among family members who are female or who live alone; those who witness the death; those whose loved ones were intubated at the time of death; and those who were not able to say goodbye to the patient. Of note, the risk of complicated grief was significantly reduced when patients requested that life-sustaining treatments be withheld30—this is an important, and perhaps under-recognized, benefit for advance care planning.

Grief and bereavement support is an important gap in healthcare services, and family members with depression or complicated grief often avoid such support, even when it is available.31 Future research should focus on developing means of better engaging and supporting family members after an ICU death.

Case 28.1 (continued)

During her fifth week of ICU stay, T.R. remains weak and dependent on dialysis and ventilation. She acutely develops severe abdominal distension and pain, melaena, confusion, and hypotension. A chest X-ray reveals free air under the diaphragm. The general surgery, ICU, and palliative care teams meet with her daughters. Through collaborative discussions, the daughters express the view that their mother would not have wanted surgery in this circumstance but instead would request comfort care with the understanding that she would die. The healthcare team supports the daughters through this decision-making process. Close family, friends, and their spiritual care provider gather, while the team provides medications and non-pharmacological interventions for comfort.

Question 13. How does withholding or the withdrawal of life support occur in the ICU?

There is no universally accepted way to withhold or withdraw life support.32 There are guidelines available for managing the clinical aspects of withholding or withdrawing life support in the ICU.33 These guidelines include many suggestions for: (1) preparing for withdrawal of life-sustaining measures; (2) assessment of distress; (3) pharmaceutical management of distress; and (4) discontinuation of life-sustaining measures and monitoring. Specific decisions must be informed by ethical, legal, philosophical, jurisdictional, religious, cultural, or idiosyncratic hospital practices.20,34 For example, the decision to extubate or simply remove ventilatory support without extubation, or the use of comfort medications in anticipation of symptoms (rather than waiting for the symptoms to appear), may be controversial in some settings, but not in others.

Future trends

Integrating the palliative approach to care in the ICU is part of the progressive expansion of palliative care throughout medicine. This integration brings with it new responsibilities and expectations for palliative care clinical teams and creates new fields for research. Future areas of study should include methods of symptom assessment and management, determining patient and family values, facilitating decision-making, aligning care plans with goals of care, and meeting the functional, emotional, spiritual, social, and financial needs of family members.[8,]33 Palliative care has the potential to supplement the care of critically ill patients, addressing the needs of patients and family members, without compromising the potential for cure or recovery.

References

1. **Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD** (2010) Critical care and the global burden of critical illness in adults. *Lancet*, **376**(9749), 1339–46.
2. **Angus DC, Barnato AE, Linde-Zwirble WT** *et al.* (2004) ICU End-of-Life Peer Group Use of intensive care at the end of life in the United States: an epidemiologic study. *Crit Care Med*, **32**(3), 638–43.
3. **Cook D, Rocker G** (2014) Dying with dignity in the intensive care unit. *N Engl J Med*, **370**(26), 2506–14.
4. **Minne L, Ameen A, de Jonge E** (2008) Evaluation of SOFA-based models for predicting mortality in the ICU: a systematic review. *Crit Care*, **12**(6), R161.
5. **Soares M, Caruso P, Silva E,** *et al.* (2010) Characteristics and outcomes of patients with cancer requiring admission to intensive care units: a prospective multicenter study. On behalf of the Brazilian Research in Intensive Care Network (BRICNet). *Crit Care Med*, **38**(1), 9–15.
6. **Vink EE, Azoulay E, Caplan A, Kompanje EJ, Bakker J** (2018) Time-limited trial of intensive care treatment: an overview of current literature. *Intensive Care Med*, **44**(9), 1369–77.
7. **Gajic O, Ahmad SR, Wilson ME, Kaufman DA** (2018) Outcomes of critical illness: what is meaningful? *Curr Opin Crit Care*, **24**, 394–400. doi: 10.1097/MCC.0000000000000530
8. **Streat SJ** (2005) Illness trajectories are also valuable in critical care. *BMJ*, **330**(7502), 1272.
9. **Coelho CBT, Yankaskas JR** (2017) New concepts in palliative care in the intensive care unit. *Rev Bras Ter Intensiva*, **29**(2), 222–30.
10. **Truog RD, Campbell ML, Curtis JR** *et al.* (2008) Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College of Critical Care Medicine. *Crit Care Med*, **36**(3), 953–63.
11. **Mercadante S, Gregoretti C, Cortegiani A** (2018) Palliative care in intensive care units: why, where, what, who, when, how. *BMC Anesthesiol*, **18**(1), 106.
12. **Hua M, Wunsch H** (2014) Integrating palliative care in the ICU. *Curr Opin Crit Care*, **20**(6), 673–80.
13. **Schulz V, Novick RJ** (2013) The distinct role of palliative care in the surgical intensive care unit. *Semin Cardiothorac Vasc Anesth*, **17**(4), 240–8.

14. **Morrison WE, Gauvin F, Johnson E, Hwang J** (2018) Integrating palliative care into the ICU: from core competency to consultative expertise. *Pediatr Crit Care Med*, **19**(8S), S86–91.
15. **Weissman DE, Meier DE** (2011) Identifying patients in need of a palliative care assessment in the hospital setting. A consensus report from the Center to Advance Palliative Care. *J Palliat Med*, **14**(1), 1–7.
16. **Nelson JE, Curtis JR, Mulkerin C** *et al.* (2013) Choosing and using screening criteria for palliative care consultation in the ICU: a report from the Improving Palliative Care in the ICU (IPAL-ICU) Advisory Board. *Crit Care Med*, **41**(10), 2318–27.
17. **Nelson JE, Puntillo KA, Pronovost PJ** (2010). In their own words: patients and families define high-quality palliative care in the intensive care unit. *Crit Care Med*, **38**(3), 808–18.
18. **McAdam J, Arai S, Puntillo K, Schuster C, Skrobik Y** (2010) Symptom control. In: Rocker G, Puntillo KA, Azoulay É, Nelson JE (eds.) *End of Life Care in the ICU from Advanced Disease to Bereavement*, p. 51. Oxford University Press, Oxford
19. **Ricks E** (2007) Critical illness polyneuropathy and myopathy: a review of evidence and the implications for weaning from mechanical ventilation and rehabilitation. *Physiotherapy*, **93**, 151–6.
20. **Devlin JW, Skrobik Y, Gélinas C** *et al.* (2018) Executive summary: clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*, **46**(9), 1532–48.
21. **Mehta S, McCullagh I, Burry L** (2009) Current sedation practices: lessons learned from international surveys. *Crit Care Clin*, **25**(3), 471–88.
22. **Krasner MS, Epstein RM, Beckman H** *et al.* (2009). Association of an educational program in mindful communication with burnout, empathy, and attitudes among primary care physicians. *JAMA*, **302**(12), 1284–93.
23. **Ten Hoorn S, Elbers PW, Girbes AR, Tuinman PR** (2016) Communicating with conscious and mechanically ventilated critically ill patients: a systematic review. *Crit Care*, **20**(1), 333.
24. **Austin CA, Mohottige D, Sudore RL, Smith AK, Hanson LC** (2015) Tools to promote shared decision making in serious illness: a systematic review. *JAMA Intern Med*, **175**(7), 1213–21.
25. **Scheunemann LP, Ernecoff NC, Buddadhumaruk P** *et al.* (2019) Clinician-family communication about patients' values and preferences in intensive care units. *JAMA Intern Med*. **179**(5), 676–84.
26. **White DB, Angus DC, Shields AM** *et al.* (2018) A randomized trial of a family-support intervention in intensive care units. *N Engl J Med*, **378**(25), 2365–75.
27. **White DB, Ernecoff N, Buddadhumaruk P** *et al.* (2016) Prevalence of and factors related to discordance about prognosis between physicians and surrogate decision makers of critically ill patients. *JAMA*, **315**(19), 2086–94.
28. **Cox CE, White DB, Hough CL** *et al.* (2019) Effects of a personalized web-based decision aid for surrogate decision makers of patients with prolonged mechanical ventilation: a randomized clinical trial. *Ann Intern Med*. **170**(5), 285–97.
29. **Seaman JB, Arnold RM, Buddadhumaruk P** *et al.* (2018) Protocol and fidelity monitoring plan for four supports. A multicenter trial of an intervention to support surrogate decision makers in intensive care units. *Ann Am Thorac Soc*, **15**(9), 1083–91.
30. **Kentish-Barnes N, Chaize M, Seegers V** *et al.* (2015) Complicated grief after death of a relative in the intensive care unit. *Eur Respir J*, **45**(5), 1341–52.
31. **Banyasz A, Weiskittle R, Lorenz A, Goodman L, Wells-Di Gregorio S** (2017) Bereavement service preferences of surviving family members: variation among next of kin with depression and complicated grief. *J Palliat Med*, **20**(10), 1091–7.
32. **Delaney JW, Downar J** (2016) How is life support withdrawn in intensive care units: a narrative review. *J Crit Care*, **35**, 12–18.
33. **Downar J, Delaney JW, Hawryluck L, Kenny L** (2016) Guidelines for the withdrawal of life-sustaining measures. *Intensive Care Med*, **42**(6), 1003–17.
34. **Cohen S, Fassier T, Azoulay E** *et al.* (2010) Withholding and withdrawal of life support. In: Rocker G, Puntillo KA, Azoulay É, Nelson JE (eds.) *End of Life Care in the ICU from Advanced Disease to Bereavement*, pp. 241–80. Oxford University Press, Oxford.
35. **Skrobik Y** (2009) Delirium prevention and treatment. *Crit Care Clin*, **25**(3), 585–92.

Chapter 29

Paediatric palliative care

Dave Lysecki and Christina Vadeboncoeur

Attitude

To enable each learner to:

- Realize the role for a palliative approach to care when a serious health condition is identified at any time in life, including *in utero*.
- View the child–family–healthcare practitioner relationship as a partnership in care.
- Recognize interventions which will support the family in a palliative approach to care throughout the life, and after the death, of the child.

Skills

To enable each learner to:

- Participate in discussions regarding serious health conditions, quality of life, and/or death in children.
- Help families identify practical ways to support all of their children, including healthy siblings.
- Assess capacity for decision-making in an adolescent.
- Demonstrate the ability to ask about atypical pain behaviours in a child with significant neurological impairment.

Knowledge

To enable each learner to:

- Summarize the information needed by healthcare practitioners to assist families in identifying goals of care and creating flexible, dynamic care plans (including birth plans).
- Recognize that children with life-threatening conditions may have difficult-to-predict courses and they and their families require support throughout the lifespan in care-related decision-making.
- Understand the role of history, physical exam, and investigations for pain of unknown origin in children with significant neurological impairment.
- Summarize the information needed in order to provide end-of-life care at home.

Case 29.1

L. and K. are the parents of J. (6 years old) and B. (3 years old) and are expecting their third child. They have been told that their fetus is a boy and has trisomy 18 and a large heart defect. They have met with a high-risk obstetrician, a geneticist, a cardiologist, and a neonatal intensivist. It is expected that the heart defect would

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be lethal without intensive care measures immediately after birth, followed eventually by one or more major surgeries. Should the infant survive the neonatal period, he would not be expected to live to adulthood and his childhood would be complicated by developmental impairments. L. (mother) and K. (father) felt strongly against the option of termination. The intensivist and cardiologist both used the term 'palliative care'.

Question 1. What is the role for palliative care when the patient is still *in utero*?

Palliative care aims to alleviate suffering. The suffering for this family has begun. L. and K. are grieving the loss of their hopes for an uncomplicated pregnancy and a healthy newborn. They suffer from receiving unexpected news and the burden of difficult decisions. They struggle with what and how to tell their other children. The children are unsure why their parents' demeanours have changed and they are worried.

Palliative care begins at diagnosis. For this family, care begins *in utero*. At this point, the parents may choose for their child to undergo intensive care, major surgeries, and aggressive life-sustaining interventions—or they may choose comfort measures only. In either scenario, a palliative approach to care is warranted to address the suffering of the family.

Question 2. What background information is important to elicit from this family on history?

It is essential to understand the parents' experience with prior pregnancies and births—have they had previous miscarriages, stillbirths, and infant loss? If so, what was their bereavement experience? Were there traumatic experiences during previous pregnancies? What were their birthing experiences? Have they had any experience with neonatal intensive care, either with their own children or with family or friends?

J. and B. will require special attention. Any health concerns? Any cognitive, behavioural, mental, or developmental concerns? How are they feeling regarding a new sibling (even before the diagnosis)? What have they been told regarding the diagnosis? If nothing, do you think they are suspicious that something is wrong? Have there been behaviour changes throughout the pregnancy so far?

Learn the key supports for the family. These may include their parents, siblings, close friends, community leaders, spiritual leaders, and health professionals. Ensure there is an invitation for these supports to be as involved in the care team as L. and K. wish.

It is also important to understand their social and financial history and, specifically, their plans for parental leave(s).

Question 3. What interventions may support a palliative approach to care?

- Parental counselling and grief support.
- Recommendations of reliable resources, references, and support groups.
- Spiritual support.
- Financial and logistics planning.
- Education and preparation for siblings.

- Assistance with communication to, and support for, extended family members.
- Care-related decision-making support.
- Birth planning, with goals of care outlined.
- Prenatal and neonatal legacy of creation/memory-making.

Question 4. How can you support this family in making a birth plan?

Attempt to learn and understand the values that hold the most importance for the family. These may be personal, family, cultural, spiritual, religious, etc. Often, this requires an understanding of their past experiences, coping strategies, and support networks. When available, these values are best explored through the use of an interdisciplinary team with a holistic focus.

Review what information L. and K. are using to understand the situation. It is important to ensure the information they have received from health professionals is consistent with the information in the medical file. If inconsistencies are present, communication or follow-up visits with specialists may be required. If they are collecting information from non-medical sources, offer to review this information alongside them and assess its validity.

Explore the parents' hopes and fears. Addressing fears helps to ensure that myths and misconceptions do not affect decisions (e.g. morphine hastens death); to educate families on how issues would be managed, should they arise (e.g. palliative sedation for intractable suffering); and to allow space for discussion and reflection on those fears that may not have easy answers (e.g. why us?). Discussing hopes allows healthcare practitioners to partner with the family to support experiences and offer treatment plans that are most likely to achieve their hopes. Hope can represent many things; this can include 'cure' or 'longer life', but also 'comfort', 'peace', and 'joyful memories'. Families may hope for a miracle up until (and sometimes after) their child's last breath. It can be therapeutic to acknowledge this hope. Healthcare practitioners can support and even share in that hope, while simultaneously encouraging families to be prepared, should that miracle not occur.

With ensuring clarity of medical information, exploring hopes, fears, and expectations, and gaining an understanding of the family's values, the healthcare team is then primed to support the parents in identifying their goals of care. By applying their goals of care to hypothetical scenarios which may arise, a family can create future care plans, in this case a birth plan.

Case 29.1 (continued)

L. and K. intend to continue with the pregnancy and delivery. They value this child's life, however short, as equal to those of other members of their family. The support of their parents is critical for them. They hold no specific religious views, but some aspects of religion are inherently tied to their culture, which is of vital importance to them.

They have been informed that, given the nature of the cardiac lesion, it is expected that the child would only live a few hours, perhaps days. This expectation is consistent with the medical records. The parents fear that they might not get to hold their infant while alive, and that their children may not get to meet their new sibling. They hope to deliver at a hospital close to home and that their child survives long enough to get home. They hope to have a birthday party at home with close family and a few ceremonial rituals and, when the time comes, that their child dies peacefully in their arms.

With the support of their team, the family makes the following birth plan:

> If L. remains healthy through the pregnancy, they wish for a vaginal delivery at their local community hospital, aware that this hospital does not have the capacity to deliver advanced neonatal care. It is their wish that the child be immediately held by L. skin-to-skin on her chest, and then transferred to K. for

skin-to-skin. They would not want neonatal resuscitation beyond stimulation and drying. They wish to attempt breastfeeding, if respiratory status allows. If the infant appears to be in respiratory failure, they would like medications for comfort and to be left alone with their child as much as possible. Should the infant be stable, they wish to be discharged home as soon as L. is medically stable.

If L. develops complications with the pregnancy, they wish for delivery at the tertiary hospital. Their care requests would remain the same. They would plan to remain in hospital until L. is cleared as safe for discharge, and would like for their child to room with them as much as possible.

L. and K. ask for a care team meeting that includes their parents. They draft a letter to extended family and friends to explain the circumstances and ask for privacy. They are counselled regarding time away from work, maternity/parental leave, and options for parents after the death of a child. They are connected with a grief counsellor and with Perinatal Hospital & Palliative Care.[1] They have a three-dimensional ultrasound done and a family pregnancy photoshoot.

J. and B. meet with a child life specialist to learn about the cycle of life and death, about trisomy 18 and their new sibling, about childbirth and the expected plans after birth, and about the normal range of emotions that families may experience during these times.

Question 5. What can be prepared to optimize the chances of achieving their goals of care?

A team meeting at the community hospital can prepare all those who may be involved. Ideally, this meeting would include members of the team responsible for the obstetric care, the team that will be responsible for the infant after birth, home care services, and a paediatric palliative care specialist team if available. Expectations, roles, and lines of communication should be clearly outlined. Teams should anticipate needs and ensure availability of, and access to, necessary medications or equipment. Written copies of the birth plan should be created and kept with the family and on the birthing unit.

Case 29.1 (continued)

At 38 weeks, L. has remained healthy and goes into spontaneous labour. They arrive at the hospital and are met by the family physician on call who has been informed of their case. She has contacted their primary physician, who offers his support as needed and intends to come in after the infant is born. They present their birth plan to the team.

Following 5 hours of labour, a baby boy is delivered. Together, they announce his name M. M. is immediately brought to her chest for skin-to-skin. He is small with a weak cry, which settles when dried, and nestled on her chest. He has increased work of breathing, but not outside of normal for a newborn. Slowly, M. changes from purple to pink. He is eventually passed to the father for skin-to-skin and then he is weighed and measured. The parents are ecstatic that he has survived the delivery, and it appears as though he will make it home.

Question 6. What symptom considerations should be taken prior to discharge home?

In M.'s case, the most important symptom to plan for is dyspnoea from congestive heart failure. Opioids and non-pharmacological measures, such as a fan, provide effective relief from the

experience of dyspnoea. Multiple non-invasive routes are available, including oral, intranasal, sublingual/buccal, and rectal. Intravenous and subcutaneous routes are additional options. It is important to counsel the parents regarding signs of dyspnoea (e.g. alert, irritable, fearful, wide eyes, pursed lips) versus increased work of breathing without dyspnoea (e.g. relaxed face or sleeping alongside ongoing indrawing, tachypnoea, gasping).

Tachypnoea/respiratory distress may also lead to an inability to tolerate oral feeds. It is beneficial to have discussed options and parental wishes in advance. In this scenario, options may include minimizing or withholding feeds, according to M.'s cues/status, or insertion of a nasogastric tube with gavage feeds.

It is likely that respiratory failure will lead to both hypoxia and hypercarbia. Hypoxia can be resolved with administration of oxygen; however, this may lead to pulmonary vasodilation and worsening of the congestive heart failure, without necessarily leading to any symptomatic benefit. Discussion with the relevant specialist (cardiology, neonatology) is warranted. Preparing the family for effects of end-stage hypercarbia may be beneficial (i.e. increased sedation).

Secretion management at end of life requires counselling and planning. Most often, upper airway noises secondary to secretions near the end of a patient's life are not distressing to the patient. With counselling on this, many families are reassured and pharmaceutical secretion management is not necessary. For families who wish to treat, atropine ophthalmic solution delivered sublingually/buccally is an easy-to-administer and effective treatment for oral secretions.[2]

It is valuable to have a benzodiazepine in the home. In the hospital setting, these drugs are readily available for emergency symptoms, however, in the home setting, this requires advance planning. Seizures are unlikely in M.'s case, but possible. More importantly, the development of agitation or perceived intolerable suffering may occur and warrant sedation. It may be useful to have midazolam available in the home, for intranasal delivery or subcutaneous infusion.

Case 29.1 (continued)

Three hours following delivery, L. is cleared to leave the hospital. They take M. home to a birthday party at their house. J. and B. are ecstatic to meet their new brother and shower him with love. Grandparents are present to cuddle and conduct an important cultural ritual. A professional photographer was arranged through a volunteer charitable organization[3] and is capturing the moments. L. and K. sleep that night with M. in their bed, devouring every precious moment.

A week later, M. is still alive and appears to be thriving. The family returns to the cardiologist for a follow-up echocardiogram. The echocardiogram demonstrates that the cardiac lesion has diminished in size from previous. There are signs of congestive heart failure, but M. is compensating.

Question 7. What are appropriate next steps for M. and his family?

With a change in the medical information, there is an opportunity to revisit the treatment plan, goals of care, and care plans. Discussion between healthcare providers is crucial to provide the family with optimal information.

The process of reviewing plans and goals of care as well as articulating a new care plan may be repeated as before:

1. Revisit values (may have changed from previous).

2. Revisit information (now more inclusive of lived experiences and daily and projected quality of life).
3. Revisit expectations, fears, and hopes, given new information.
4. Revisit goals of care.
5. Revisit care plans.

Case 29.2

A. is a 17-year old with a localized osteosarcoma of her left femur diagnosed at age 13. Treatment included chemotherapy, followed by surgical resection, and then further chemotherapy. Each course of chemotherapy was complicated by pain at the tumour site and severe nausea. Post-operatively, she had phantom limb pain, nausea, and infection. Follow-up scans 6 months after completion of her therapy revealed nodules in her lungs which were surgically resected and found to be malignant. After a further 12 months, a new lesion in her liver was confirmed to be metastatic disease.

A. and her parents are at an appointment with you for other reasons, when A. states that she does not want any further therapy; she just wants to finish school and to travel. A.'s parents are taken by surprise and tell her that, of course, she will get further therapy.

Question 8. How would you assess A.'s capacity to decline treatment?

In all Canadian provinces and territories, the determining factor in a child's ability to provide or refuse consent is whether the young person's physical, mental, and emotional development allows for a full appreciation of the nature and consequences of the proposed treatment or lack of treatment.[4]

You need to be reasonably confident that the youth understands the nature of the proposed treatment and its anticipated effect, as well as the consequences of refusing treatment. One way to gauge this capacity is to use the teach-back technique—ask the youth to re-phrase what they have just been told and invite the youth to ask questions. More complex medical situations may require more rigor in determining whether the youth understands. It is prudent for physicians to also encourage the youth to invite a family member to attend the discussion.

Question 9. How would you approach the discussion between A. and her parents about further therapy?

Consider using the '*Serious illness conversation guide for pediatrics*', which provides a framework of parent-tested language to discuss worries or fears in order to determine the best plan of care.[5]

Case 29.2 (continued)

Following discussions, A. decided to enrol in a Phase I therapeutic trial in an attempt to control her disease, with the goal of graduating from high school. However, her disease continued to progress, and she and her parents wish to remain home as much as possible. She asks whether she can be at home for her end-of-life care and specifically asks how her pain will be managed.

Question 10. How would you approach discussion of end-of-life planning with A.?

- The approach from the *Serious Illness Conversation Guide for Pediatrics* can be used here as well.
- Many adolescents/young adults express fears of being forgotten or about not having made a difference in the world.
- Many young people worry about how their parents, siblings, and friends will cope after they have died. Specifically asking if they have worries about their loved ones can open lines of communication.
- Many people have specific worries about the dying process or what happens after death. Explore this by letting the youth lead the discussion and respecting family and individual cultural, religious, and spiritual beliefs.
- There are tools that may help the youth to plan, including '*Voicing My CHOICES: A planning guide for adolescents & young adults*'.[6]

Question 11. Are there valid tools for assessment of pain in children?

There are many validated assessment tools for pain in children of all ages. The most commonly used are the Numerical Rating Scale, which is a self-report scale validated for children older than 6 years of age. The Faces Pain Scale—Revised[9] (see Figure 29.1) uses pictorial representations of pain and can be taught to children as young as 3 or 4. For non-verbal children, the FLACC pain assessment tool[10] (see Table 29.1) is an observer-rated pain scale. For more specialized pain scales in non-verbal children, see the American Academy of Pediatrics clinical report '*Pain assessment and treatment in children with significant impairment of the central nervous system*'.[7]

Question 12. What integrative strategies can be used when children have pain?

Supportive and integrative (non-pharmacological) strategies have been shown to reduce pain in children and make pharmacological management more effective.

- Physical methods (e.g. cuddle/hug, massage, comfort positioning, heat, cold, transcutaneous electrical nerve stimulation).
- Cognitive behavioural techniques (e.g. guided imagery, hypnosis, abdominal breathing, distraction, biofeedback).
- Acupuncture, acupressure, and aromatherapy.

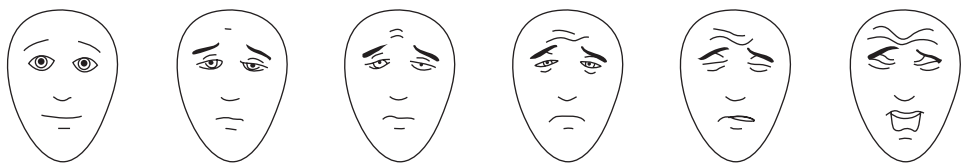


Fig. 29.1 Faces Pain Scale—Revised.

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Table 29.1 FLACC pain assessment tool

Categories	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractable	Difficult to console or comfort

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Question 13. What pharmacological strategies are effective in treating pain in children?

Over-the-counter analgesics, such as acetaminophen and ibuprofen, can be effective on their own or in conjunction with opioids for moderate to severe pain. There are many resources to guide opioid dosing in children. Being familiar with your paediatric referral centre's guidelines or reaching out for assistance with complicated medical situations can be helpful. It is also helpful to review myths and misconceptions about opioids with the family, as well as common and uncommon side-effects, which are similar to those in adults.

Adjuvant medications, such as low-dose antidepressants, anticonvulsants, and antispasmodics, can be effective in treating pain. Consultation with a paediatric colleague or a paediatric palliative care physician who is experienced in using adjuvant medications may be helpful.

Question 14. What are the things that need to be considered to ensure A. can be at home for as long as possible?

Discussion of location of care is important. People generally prefer to die where they are most comfortable. For most, this is at home. However, others may feel more comfortable in a hospital where they have spent much of their treatment time, or in a hospice which can provide skilled medical care in a home-like environment. Some wish to be at home for as long as possible, but to be transferred to hospital or hospice when death is imminent.

Feasibility of care at home can be explored by examining the resources in your area such as access to professional support (e.g. available physician support, visiting/shift nursing) and availability of equipment (e.g. hospital bed, intravenous pumps). In some cases, as end of life approaches, rapidly increasing care needs make care at home difficult and alternate arrangements must be made.

It is important to discuss in advance with the patient and family details about who is able to confirm death, complete the death certificate, and support the family in practical arrangements such as choice of a funeral home and details about memorial services or funerals.

A discussion of the possibility of organ/tissue donation may need input from an agency to determine candidacy. A discussion about whether an autopsy may provide additional information about the youth's illness can be done in advance. If desired, details about costs of transport from home to hospital for autopsy should be determined in advance, as they may influence the location of end-of-life care.

Case 29.3

R. is a 6-month-old child born to a 34-year-old woman and her 36-year-old partner. R. had seizures after birth and was not developing normally. A work-up confirmed a rare genetic condition described as 'neurodegenerative', with an expected prognosis of between 2 and 8 years. His two older siblings are genetically not affected. He is in your office for his 6-month immunization and this is the first time you have seen the family since the diagnosis was confirmed.

Question 15. How can you assess how well the family's needs are being met?

Topics which are important to discuss include:[8]

- Education—ensure they have adequate information on the child's diagnoses and treatments (including complementary or integrative therapies). Are the family aware of the genetic implications on future pregnancies?
- Quality of life—discuss opportunities for joy, experience of suffering, and adjustment to illness/'new normal'.
- Home care—explore the adequacy of caregivers and equipment in the home, transitional care facilities, and hospice services.
- Communication—ensure the family feels there is open two-way communication, including regarding prognosis and goals of care.
- Finances—explore medical costs, insurance coverage, food security, utilities, and housing.
- Care planning—engage in discussions, as appropriate, including 'do not resuscitate' conversations and end-of-life decision-making.
- Family support—inquire about including sibling coping, grandparent care, and couple's concerns.
- Spiritual—explore spiritual health and meaning-making.
- Counselling—explore needs for help with anger, depression, and anxiety.
- Transportation—explore access to transportation requirements.

Case 29.3 (continued)

R.'s parents describe periods of time when he is inconsolable for hours at a time. They have tried acetaminophen and ibuprofen individually and together, but he does not improve. They take turns holding R., but nothing seems to comfort him. These episodes occur every other day and have been evident for the past 3 months.

Question 16. How can you determine whether R. has pain?

The FLACC pain scale is most easily used by observers on non-verbal children. Children who have neurologic impairment can exhibit different patterns of behaviour than other children in association with pain or discomfort, which can be difficult to interpret when the child is also non-verbal. The revised version[10] (rFLACC; see Table 29.1) allows parents to add custom items specific to their child's individual cues. Some of these behaviours include:[7]

- Vocalizations (crying, whimpering, moaning, gasping, sharp intake of breath).
- Facial expression (grimacing, frowning, furrowed brow, squinting, eyes wide open, clenched teeth, teeth grinding, distressed look).
- Consolability (inability to be consoled and made comfortable).
- Interaction (withdrawn, seeking comfort).
- Sleep (disturbed sleep, increased or decreased sleep).
- Movement (increase from baseline in movement of arms and legs, restless and fidgety, startles easily, pulls away when touched, twists or turns).
- Tone (stiffening of extremities, clenching of fists, back arching, resists movement).
- Physiologic (tachycardia, sweating, shivering, change in colour, pallor, breath-holding, tears).
- Atypical features (blunted facial expression, laughter, breath-holding, self-injurious behaviours).

There are other longer tools which can be used, which can be even more individualized for the child.[7]

Question 17. What specific assessment of R. can be completed to determine if there is a known cause for his irritability?

A complete, directed physical examination should be completed, with specific attention to:[7]

- Eyes (tears, conjunctival injection, corneal abrasion).
- Dentition, mouth, and throat (dental caries and abscess, gingivitis, tonsillitis).
- Inspection and palpation of shunt catheter site if appropriate (ventriculoperitoneal shunt malfunction).
- Inspection and movement of gastrostomy tube to assess the fit (which may change with growth).
- Inspection and palpation of his abdomen (constipation, distension).
- Inspection of skin (hair tourniquet or pressure ulcer).
- Inspection, palpation, and movement of extremities (occult fracture).
- Palpation and range of motion of joints (subluxation, especially hips).

Question 18. You have completed a directed history and physical examination and have found no identified source for the discomfort but believe R. is having pain. What treatments might you consider?

Gabapentinoids are the usual first choice for treatment of recurrent pain behaviours in this clinical situation when there are three or more prolonged episodes per week or a monthly cycle of frequent

episodes for 1–2 weeks each month. Gabapentin or pregabalin are usually titrated up[7] gradually to prevent transient drowsiness unless pain is severe. Choice of medication is dependent on local availability in a liquid form where needed, and medication coverage issues if cost is prohibitive.

Second-line medications (usually added to first line) include tricyclic antidepressants (amitriptyline or nortriptyline), opioids, or clonidine.

If pain behaviour continues, consider referral to a paediatrician or paediatric palliative care team with experience in managing pain and discomfort in children with significant neurologic impairment.

Case 29.3 (continued)

During the discussion of R.'s quality of life, his parents ask you about prognosis and how to maximize his quality of life.

Question 19. How do you explore care planning with R.'s parents?

In children with rare diseases, prognosis is often varied or even unknown. The philosophy of 'hoping for the best, but planning for the worst' is an approach that many families find useful. In infancy, discussion of scenarios where the child may lose the ability to swallow is important for planning purposes. There are loving, caring families who decide not to intervene with feeding tubes and accept the increased risk of aspiration as they place high value on the benefit of continued oral stimulation. In this case, it is important for the parents to be aware that while this choice is valid, if there are settings where others will be responsible for feeding (e.g. at daycare or at school), these non-family carers may not feel safe providing oral feeding, so a plan discussed in advance may be very helpful to prevent conflict if the situation arises.

Discussion of eligibility for daycare and/or school is important, as these facilities may need advance notice in order to best meet the care needs of the child.

Discussion of emergency treatments for a sudden deterioration is helpful. It is important to recognize that, despite a life-limiting/life-threatening condition, many families may wish for life-sustaining interventions for acute, reversible, superimposed conditions (e.g. influenza, medication error). However, even for potentially reversible, superimposed conditions, some families choose to allow natural death when the deterioration is associated with the underlying disease process (e.g. aspiration pneumonia) or the treatments themselves may lead to additional complications (e.g. major surgery).

It is important to remember that discussions about care planning are not a one-time event but should occur periodically, particularly at times when the child's medical condition changes (either improves or deteriorates). If your location has specific advance care documentation, it is important that the family has up-to-date documentation and that all caregivers understand that decisions in the moment may change from even the most recent documentation.

Children with life-limiting illness may be eligible for a 'wish'. Reaching out to the foundations that provide these wishes is helpful, so that you and the family are aware of the eligibility criteria, which will include the diagnosis and medical determination of eligibility but may also include parameters such as age and the need for medical attendants during the wish.

References

1. **Perinatal Hospice & Palliative Care**. https://www.perinatalhospice.org
2. **Rapoport A** (2010) Sublingual atropine drops for the treatment of pediatric sialorrhea. *J Pain Symptom Manage*, **40**(5), 783–8.
3. **Now I Lay Me Down To Sleep**. www.nowilaymedowntosleep.org
4. **Canadian Medical Protective Agency** (2014; revised June 2016) *Can a child provide consent?*
5. **Van Breeman C** (2018) Adapting the serious illness conversation guide for use in pediatrics. *J Palliat Med*, **21**(12), 1683.
6. **Aging with Dignity**. *Five Wishes: Voicing my CHOICES*. https://fivewishes.org
7. **Hauer J**, **Houtrow AJ**, **Section on Hospice and Palliative Medicine, Council on Children with Disabilities** (2017) Pain assessment and treatment in children with significant impairment of the central nervous system. *Pediatrics*, **139**(6), e20171002.
8. **Weaver MS**, **Schroeder D**, **Wichman C**, **Bace S**, **Vail C**, **Macfadyen A** (2017) Pediatric palliative care needs assessments: from paper forms to actionable patient care. *J Palliat Med*, **20**(3), 216–17.
9. **Hicks CL**, **von Baeyer CL**, **Spafford PA**, **van Korlaar I**, **Goodenough B** (2001) The Faces Pain Scale—Revised: toward a common metric in pediatric pain measurement. *Pain*, **93**(2), 173–83. doi: 10.1016/S0304-3959(01)00314-1
10. **Merkel SI**, **Voepel-Lewis T**, **Shayevitz JR**, **Malviya S** (1997) The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs*, **23**(3), 293–7.

Chapter 30

Palliative care for structurally vulnerable populations

Naheed Dosani and Anna Voeuk

Attitude

To enable each learner to:

- Consider ethical issues and equity pertaining to provision of palliative care for structurally vulnerable populations (SVPs).
- Support cultural safety as a central component of equity-informed palliative care.
- Recognize one's own beliefs, values, and biases and how they might affect assessment and treatment of patients dealing with deficiencies in the social determinants of health (SDoH).

Skills

To enable each learner to:

- Apply concepts and initiate a palliative care approach to populations with structural vulnerability.
- Use tools to advocate for patients at the micro-, meso-, and macro-levels to improve health outcomes.
- Develop an awareness of one's own biases that can affect how patients and families are treated when dealing with inequity.

Knowledge

To enable each learner to:

- Define and describe the impact that structural vulnerability has on populations needing palliative care.
- Use tools to apply an SDoH approach to palliative care delivery.
- Formulate a foundation in trauma-informed approaches to palliative care.
- Recognize the social and ethical complexities of caring for SVPs.

Case 30.1

J.J. is a 62-year-old white female. She has required transitional housing at a local shelter for the last 22 months and shares a dorm room with 14 other women. Previously, J.J. owned her own business and was a single mother to her daughter A.B. Approximately 2 years ago, A.B. died of an opioid overdose. After her death, J.J. developed a substance use disorder and, due to circumstances that were out of her control, fell into poverty. Without other systems of support around her, she became street homeless but was able to find temporary

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shelter via the transitional housing programme. One day, J.J. developed severe and unrelenting hip pain. When she sought medical attention at the local hospital's emergency department, she felt unheard and discriminated against, particularly because of her past history of substance use and homelessness.

Question 1. What are the 'social determinants of health'? How do they relate to the concept of 'structural vulnerability'?

The SDoH define a particular classification of social and economic components of individual, social, economic, and environmental aspects that influence both individual and population health,[1] including income, housing, employment, and education.[1,2] Structural vulnerability is a concept that explicitly recognizes the effects of the SDoH on health outcomes. Populations are ' … structurally vulnerable when their location in their society's multiple overlapping and mutually reinforcing power hierarchies (e.g. socioeconomic, racial, cultural) and institutional and policy-level statuses (e.g. immigration status, labor force participation) constrain their ability to access healthcare and pursue healthy lifestyles.'[3]

Structural vulnerability urges us to look beyond an individual's behaviour to understand his/her location in socio-economic, political, and cultural hierarchies, and the vulnerabilities produced as a result of that structural arrangement. For example, SVPs often face significant barriers to care, including a broader focus on their needs pertaining to the SDoH.[4] We can think of SVPs as those whose access to healthcare and decision-making are constrained as a result of residing on the lower end of society's hierarchies. That is, the concept of structural vulnerability moves away from placing individual blame on those who suffer and recognizes a broader context in which the problem is more about external forces (e.g. poverty, homelessness, colonization) and assumptions that individuals are at fault.[4]

Question 2. What structural vulnerabilities is J.J. dealing with? How do they impact her care?

J.J. is homeless, which can be defined as a 'situation of an individual, family or community without stable, safe, permanent or appropriate housing … '[5] Further, the definition recognizes that homelessness is often 'the result of systemic or societal barriers, a lack of affordable and appropriate housing and/or financial, mental, cognitive, behavioural or physical challenges … '[5] Homelessness can be characterized as a variety of housing and shelter conditions such as unsheltered, emergency sheltered, provisionally accommodated, and at risk of homelessness.[5] For most, homelessness is not experienced as a static state, as one's housing circumstances may shift along a spectrum of conditions.[5] Recent work defines more specifically Indigenous homelessness in the Canadian context.[6]

Homeless individuals have been shown to have more ageing-related illnesses, compared to those who have stable homes. One study[7] shows they are 29 times as likely to have hepatitis C, five times as likely to have heart disease, and four times as likely to have cancer. Further, this population typically lives half as long as housed populations.[8]

Other structural vulnerabilities impacting J.J. include poverty, social isolation, a history of substance use, and trauma.

Question 3. How does trauma impact J.J.'s engagement with healthcare?

Persistent homelessness, her daughter's death, a history of substance use, and discrimination when interacting with the healthcare system are all potential trauma experiences for J.J.

Trauma describes 'an experience that creates a sense of fear, helplessness, or horror, and overwhelms a person's resources for coping.'[9] For example, an accident/injury, sexual violence, or a diagnosis of a medical illness can be considered forms of trauma. However, greater recognition of the way that structural vulnerabilities (e.g. racism, homophobia) can lead to direct and indirect exposures to trauma exists.[10] For example, victimization and traumatic stress associated with homelessness lead to underlying trauma and are so interconnected, making it impossible to address care for this population without consideration of trauma.[9,10] Ganzel[11] (citing McFarlane) reports that exposure to trauma is a predictor of poor health outcomes and increased mortality. Symptoms of trauma can include hyperarousal, hypervigilance, and emotional numbing.[10,11] Trauma can severely impact an individual's ability to develop positive and trusting relationships over an entire lifetime.[10,11] This can impact the ability to create trusting and therapeutic relationships with healthcare providers.

Given J.J.'s experiences with trauma, engaging her in a trauma-informed care (TIC) approach is important. TIC encompasses several approaches, which include, according to Hopper, Bassuk, and Olivet[9] (citing Moses, Reed, and Mazalis), ' … understanding, anticipating, and responding to the issues, expectations and special needs that a person who has been victimized may have in a particular setting or service.' Organizations supporting TIC institute policies and procedures that seek to prevent retraumatization or blaming and to manage traumatic responses.[11]

Case 30.1 (continued)

J.J.'s pain becomes so severe that she now decides to seek help at a local primary care clinic, but again feels unwelcome because of how she is treated and because she is not offered further investigations that she feels she needs. Without anyone to turn to, J.J. turns to the use of street-drugs, including crack-cocaine and fentanyl, to manage her symptoms. In pain crisis, J.J. goes to hospital and demands further work-up. Diagnostic imaging shows she has end-stage metastatic breast cancer.

Question 4. What are the challenges that SVPs face in receiving equitable access to palliative care?

Due to structural vulnerabilities, the homeless population is often unable to access palliative care until late in their illness, and commonly not at all. They have fewer social supports and often die alone, in acute healthcare or shelter settings or transitional spaces (e.g. sidewalk, park, alleys), despite studies indicating that 'homeless people fear dying anonymously or undiscovered.'[4] The homeless also face significant challenges in discussing palliative care with social service health providers. They fear discrimination at end of life, resulting from previous experiences interacting with the medical system, as reported by Stajduhar, Mollison, Giesbrecht, et al.[4] (citing Ko *et al.*).

A Canadian study,[4] focused on the experiences of SVPs at end of life, highlights five challenges to equitable access to palliative care, which include:

1. De-prioritization of palliative care due to a need to focus on day-to-day survival.

2. Normalization of death, as many either do not see themselves within a 'dying trajectory' or assume that the lifestyle of homelessness will cause death.
3. Complexities of identifying those with palliative care needs because this population often receives care outside of formal health and medical systems (e.g. social care workers).
4. Concerns by service providers regarding workplace risk and safety when serving SVPs.
5. Siloing of care systems, creating confusion regarding who is responsible for initiating a palliative approach to care.

Question 5. How may this case be different if J.J. identified as Indigenous?

Canada's long-standing colonial history, including residential schools, assimilationist policies, and medical discrimination, has led to widespread disparities in health outcomes between Indigenous and non-Indigenous populations.[12] Similar disparities are seen in the delivery of palliative care in the nearly 618 Indigenous communities in Canada.[13] Limited health and medical services, as well as culturally safe services, are additional barriers to accessing palliative care services.[12,13] Indigenous people who leave their homes to access palliative care may experience further feelings of isolation during the end of life. Those who die outside of their community may also experience many other harmful effects.[13]

Colonization has created a legacy of dispossession in which Indigenous people have systematically been separated from their homeland, languages, and families. It is important to recognize the impacts of dispossession and racism on J.J.'s ability to access palliative care and supports otherwise provided by family and community. Beyond a TIC approach, a culturally safe approach to caring for her and the community she has chosen would be vital.

Question 6a. How might this case be different if this were a Syrian refugee who recently arrived in Canada?

The United Nations Refugee Convention defines a refugee as 'someone who is unable or unwilling to return to their country of origin owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group, or political opinion.'[14] Refugees seek protection in other countries as they flee from violence, persecution, or conflict. Awareness that this person and her family spent years in an overcrowded refugee camp in Jordan, a neighbouring country hosting Syrian refugees after the civil war began in 2011, provides context. For example, access to quality healthcare was limited after the conflict began.

Question 6b. What SDoH leading to structural vulnerability should be considered?

Language and communication

Ideally, a professional or trained interpreter would be present to help patients deliver information in their preferred language to ensure they have the opportunity to make informed decisions. Certain expressions and idioms may reflect issues associated with psychological and social problems and physical symptoms.[15] Some patients may feel obligated or pressure to have family members or friends interpret out of perceived convenience or feelings of no choice. However, this can be problematic, as issues of confidentiality and sensitivity may arise.

Finances, housing, and healthcare

This person may have resettled in Canada through the private sponsorship of a local church group. From 2015 to 2018, Canada welcomed an estimated 58 650 Syrian refugees, including those who are: Canadian government-assisted, privately sponsored through a group of people or organization, or receiving blended sponsorship.[16] Government-sponsored Syrian refugees who arrived early during the crisis in 2014 faced difficulties with temporary housing and the challenge of finding more permanent and affordable housing. Many refugees have difficulty getting jobs, but those who work send money back to their home country to support relatives. Syrian refugees have healthcare coverage for up to 1 year through the Interim Federal Health Program (IFHP),[17] until they receive their provincial/territorial healthcare card. Private sponsors are responsible for covering most expenses for up to 1 year or until securing employment.

Social supports

The sponsoring group provides social support such as registering children in school, connecting newcomers with a primary care physician, helping set up a bank account, and orienting to life in Canada. Social networks and belonging in a community provide support needed for patients and their families.

Faith/spirituality

In order to determine how best to address spiritually related issues or suffering, knowing that faith is important to a person is helpful. Syrian refugees in Jordan have reportedly relied on faith as a coping mechanism for dealing with challenges.[18] Some Syrians may have been persecuted on the basis of their religion and thus may be reluctant to discuss their spiritual beliefs openly with anyone they do not trust for fear of possible repercussions. Reassuring people that they have the freedom to practise their beliefs without harm helps them develop trust with you and the spiritual care team.

Trauma

Refugees who are especially vulnerable include: unaccompanied children; those who faced sexual and gender-based violence or torture; people with disabilities; and older populations.[19] Evidence-based guidelines for refugees and immigrants recommend against routine screening for traumatic events in patients who are functioning well, since persuading patients to disclose details of traumatic events may be more harmful.[20] However, clinicians should be aware of signs and symptoms that may point to evidence of post-traumatic stress disorder or depression and provide further assessment and management.[19,20]

Question 6c. What other considerations exist if the patient were a migrant from another country?

Migrants are defined as people who move from their usual place of residence across international borders or within a country, regardless of legal status, involuntary or voluntary reasons, the impetus for moving, or the duration of stay.[21] They may be at risk of health issues, depending on various SDoH (e.g. employment, race, education, disability). Immigrants, asylum seekers (those looking for protection from persecution in another country and having applied for refugee status[21]), and non-status or stateless people all face the potential of dealing with issues affecting their health.

Question 7. How do we support J.J. while acknowledging her substance use?

SVPs, including the homeless and vulnerably housed, have consistently been described as consuming alcohol and/or illicit drugs at rates higher than housed Canadians.[22] Further to poor health outcomes associated with structural vulnerabilities like lack of housing, substance use is another contributor to morbidity and mortality.[22] This population often lacks access to palliative care, since a common expectation is for drug users to abstain from use at the end of life.[22] The widespread adoption of abstinence-based policies by palliative care providers and their agencies is viewed as discriminatory and has led to drug users coast-to-coast dying without proper care or support.[22,23]

The Canadian Mental Health Association[24] (citing Thomas), states that harm reduction can be defined as '… an evidence-based, client-centred approach that seeks to reduce the health and social harms associated with addiction and substance use, without necessarily requiring people who use substances from abstaining or stopping.' Furthermore, '[e]ssential to a harm reduction approach is that it provides people who use substances a choice of how they will minimize harms through non-judgemental and non-coercive strategies in order to enhance skills and knowledge to live safer and healthier lives.'[24]

A harm reduction approach to care for J.J. could include open and non-judgemental discussions about her drug use, the promotion of harm reduction best practices, and recognition of the complexities of symptom management when dealing with addiction.

Case 30.1 (continued)

J.J. is now taking opioids prescribed via a consistent physician to control her pain. She is also currently on the list to receive community-based palliative care services. However, as her housing status is precarious (i.e. she lives in transitional housing and has only 2 months left in her agreement) and is progressively becoming more ill, she realizes that she is again at risk of being street-homeless. While the shelter provides her with daily meals, she learns that she cannot receive palliative care there because healthcare providers and other people providing support are not allowed to enter the building. While transitional housing provides J.J. with shelter, the policies in place are restricting her from receiving the care she needs, which puts her in a more vulnerable position.

Question 8. How can we advocate for supporting J.J.'s structural vulnerabilities?

Throughout history, physicians and other health providers have been called to go beyond the bedside to provide moral and socially just care in the spirit of advancing human society and the human condition. According to Buchman, Woollard, Meili, and Goel[25] (citing Dharamsi, Ho, Spadafora, and Woollard), '*[s]ocial accountability* is the social contract that medicine has with society.'[25] This should promote equitable access to care that is responsive to a client and community's needs. Palliative care providers caring for SVPs have an opportunity to advocate for the clients they serve. One model[25,26] describes three levels of social accountability as:

- The individual level (micro).
- The community level (meso).
- The public, policy, and population level (macro).

Depending on J.J.'s goals, at the micro-level, you could screen for poverty and homelessness and then recommend social 'treatments' to address these deficiencies. At the meso-level, you could advocate by organizing education sessions to support care providers working with clients with SVPs. In some Canadian cities like Victoria, Calgary, and Toronto, community advocacy groups organize homeless memorials to commemorate the lives of those lost and bring attention to the advocacy needed to improve conditions for SVPs. At the macro-level, teams with a special focus on providing palliative care for people like J.J. could work together to present policy or position statements (e.g. improved funding for affordable housing) to provincial and/or federal government. Grassroots advocacy groups like Health Providers Against Poverty (HPAP) and Canadian Doctors for Refugee Care are examples of how social accountability can be framed at the macro-level.

Case 30.1 (continued)

Through advocacy via J.J.'s healthcare providers and service care providers, the local home and community care programme agree to make a 'special case' to provide palliative care services to her in her transitional shelter unit. J.J. dies, peacefully, surrounded by her street family, at what she considered to be her home.

Question 9. What innovative models of care can be utilized to support SVPs in need of palliative care?

A patchwork of programmes have developed across Canada to meet the unique palliative care needs of SVPs. Mobile outreach programmes consisting of interdisciplinary teams (e.g. case workers, peers, nurses, physicians) have been established in some Canadian cities like Victoria, Calgary, Edmonton, and Toronto. As a further response, providers and their organizations have established dedicated palliative care beds for SVPs via models such as surrogate housing and hospice. Finally, homeless and palliative care advocacy groups have produced evidence-based toolkits to provide information and resources to frontline staff supporting homeless populations providing palliative care.[27]

Conclusions and future directions

Although this case focuses on individuals who are homeless in Canada, it highlights similar issues that palliative care teams might need to consider when dealing with patients and families in other contexts who may have structural vulnerabilities. Awareness of your own assumptions, beliefs, values, and biases will help remind you take an approach that is culturally sensitive and appropriate. This also helps to avoid developing prejudices or perpetuating stereotypes of certain groups of people based on ethnicity, gender, culture, language, behaviours, and religious/spiritual background. Recognizing the SDoH and factors leading to structural vulnerability of populations provides a better understanding of how they might affect a person's health and equitable access to high-quality palliative care.

References

1. **Government of Canada** (2020) *Social determinants of health and health inequalities*. https://www.canada.ca/en/public-health/services/health-promotion/population-health/what-determines-health.html
2. **Raphael D**, **Bryant T**, **Mikkonen J**, **Raphael A** (2020) *Social Determinants of Health: The Canadian Facts*, 2nd edn. York University School of Health Policy and Management, Toronto. http://www.thecanadianfacts.org/

3. **Bourgois P**, **Holmes SM**, **Sue K**, **Quesada J** (2017) Structural vulnerability: operationalizing the concept to address health disparities in clinical care. *Acad Med*, **92**(3), 299–307.
4. **Stajduhar KI**, **Mollison A**, **Giesbrecht M** *et al.* (2019) 'Just too busy living in the moment and surviving': barriers to accessing health care for structurally vulnerable populations at end-of-life. *BMC Palliat Care*, **18**(1), 11.
5. **Canadian Observatory on Homelessness, Gaetz S**, **Barr C**, **Friesen A** *et al.* (2012) *Canadian definition of homelessness*. https://www.homelesshub.ca/resource/canadian-definition-homelessness
6. **Canadian Observatory on Homelessness, Thistle J** (2017) *Definition of Indigenous homelessness in Canada*. https://www.homelesshub.ca/IndigenousHomelessness
7. **Street Health and the Wellesley Institute** (2007) *The Street Health report 2007*. https://www.wellesleyinstitute.com/wp-content/uploads/2007/09/Street-Health-Report-2007.pdf
8. **Stajduhar K**, **Mollison A**, **Giesbrecht M** *et al.* (2018) *Too little, too late: how we fail vulnerable Canadians as they die and what to do about it*. University of Victoria Institute on Aging and Lifelong Health, Victoria. https://www.uvic.ca/research/groups/peol/assets/docs/too-little-too-late.pdf
9. **Hopper EK**, **Bassuk EL**, **Olivet J** (2010) Shelter from the storm: trauma-informed care in homeless services settings. *Open Health Serv Policy J*, **3**, 80–100.
10. **Skinner E**, **McNaughtan A**, **Ahmed A** *et al.* (2018) *Trauma-informed palliative care with the homeless workbook*. https://www.ottawainnercityhealth.ca/wp-content/uploads/2018/10/TIC-Workbook-08_04_2018_ed.pdf
11. **Ganzel BL** (2018) Trauma-informed hospice and palliative care. *Gerontologist*, **58**(3), 409–19.
12. **Schill K**, **Caxaj S** (2019) Cultural safety strategies for rural Indigenous palliative care: a scoping review. *BMC Palliat Care*, **18**(1), 21.
13. **Kelley ML**, **Prince H**, **Nadin S** *et al.* (2018) Developing palliative care programs in Indigenous communities using participatory action research: a Canadian application of the public health approach to palliative care. *Ann Palliat Med*, **7**(Suppl 2), S72.
14. **United Nations High Commissioner for Refugees** (2010) *Convention and protocol relating to the status of refugees*. https://www.unhcr.org/3b66c2aa10.html
15. **Hassan G**, **Kirmayer LJ**, **Mekki-Berrada A** *et al.* (2015) *Culture, context and the mental health and psychosocial wellbeing of Syrians: a review for mental health and psychosocial support staff working with Syrians affected by armed conflict*. www.unhcr.org/55f6b90f9.pdf
16. **Immigration, Refugees and Citizenship Canada** (2018) *Syrian refugees family composition—ad hoc IRCC (specialized datasets)*. https://open.canada.ca/data/en/dataset/ca243c40-a6d3-4a46-a578-b4fad4369df0
17. **Government of Canada** (2018) *Interim federal health program policy: review the policy*. https://www.canada.ca/en/immigration-refugees-citizenship/corporate/mandate/policies-operational-instructions-agreements/interim-federal-health-program-policy.html
18. **Pinheiro I**, **Jaff D** (2018) The role of palliative care in addressing the health needs of Syrian refugees in Jordan. *Med Confl Surviv*, **34**(1), 1938.
19. **Pottie K**, **Greenaway C**, **Hassan G**, **Hui C**, **Kirmayer LJ** (2016) Caring for a newly arrived Syrian refugee family. *CMAJ*, **188**(3), 207–11.
20. **Pottie K**, **Greenaway C**, **Feightner J** *et al.* (2011) Evidence-based clinical guidelines for immigrants and refugees. *CMAJ*, **183**(12), E824–925.
21. **International Organization for Migration** (2018) *Key migration terms*. https://www.iom.int/key-migration-terms
22. **McNeil R**, **Guirguis-Younger M** (2012) Illicit drug use as a challenge to the delivery of end-of-life care services to homeless persons: perceptions of health and social services professionals. *Palliat Med*, **26**(4), 350–9.

23. **McNeil R**, **Guirguis-Younger M**, **Dilley LB** (2012) Recommendations for improving the end-of-life care system for homeless populations: a qualitative study of the views of Canadian health and social services professionals. *BMC Palliat Care*, **11**, 14.
24. **Canadian Mental Health Association** (2019) *Harm reduction*. https://ontario.cmha.ca/harm-reduction/
25. **Buchman S**, **Woollard R**, **Meili R**, **Goel R** (2016) Practising social accountability: from theory to action. *Can Fam Physician*, **62**(1), 15–18.
26. The College of Family Physicians of Canada (2018) *The CFPC social justice lens*. https://www.cfpc.ca/social_accountability_working_group_references_resources/
27. **Kennedy P**, **Hudson BF**, **Shulman C**, **Brophy N** (2018) *A toolkit for supporting homeless people with advanced ill health*. https://www.homelesspalliativecare.com

Chapter 31

Methadone

Pippa Hawley

Attitude

To enable each learner to:

- Identify when methadone is an appropriate choice of analgesic.
- Understand the reasons for prejudice against use of methadone and the importance of ensuring equitable access to it.

Skills

To enable each learner to:

- Formulate a plan for commencement of methadone in a non-urgent setting.
- Be able to counsel patients on precautions to follow when taking methadone for pain.

Knowledge

To enable each learner to:

- Describe the pharmacological properties of methadone and its side-effects.
- List the most clinically important interactions between methadone and other drugs.

Case 31.1

M.K. is a 46-year-old male with metastatic renal cell cancer. He has metastasis in the sacrum and a large mass at the left nephrectomy site, which is invading the vertebrae and encroaching on the spinal cord. He has had maximal radiation to both sites, and the spinal surgical service have said that his disease is not operable. The mass is too large for cryoablation and is wrapped round the aorta. He also has multiple lung metastases. Palliative chemotherapy had to be discontinued because of renal impairment and peripheral neuropathy. He has just started on an immune therapy with palliative intent. His oncologist has referred M.K. to you for assistance with pain management. He is taking Hydromorph Contin 21 mg q12h, and 4 mg of short-acting hydromorphone three or four times a day depending on his activity level. He says the breakthrough used to work well but it is getting less effective, and the pain in his back is spreading. He has burning and numbness over the left flank, and severe sharp pain in the mid-thoracic spine and low back when he tries to walk. He has frequent myoclonic jerks and has been having some vivid nightmares.

M.K. lives with his wife and two teenaged children. His wife is a social worker. He is willing to accept the side-effects of anti-cancer treatments if they might help him live longer, but also understands that his life expectancy is short and wants to be at home, so long as his wife and family can cope.

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Question 1. Before we talk about methadone, what are some important considerations related to the context in which cancer patients need palliative care?

The advent of personalized oncogenomic analysis and new immune therapies has led to newsworthy reports of genuinely amazing responses in oncology. Many patients hold out great hopes for these treatments despite actual response rates being disappointingly low. Patients maintain close contact with oncology services at a stage of illness where they would normally be discharged to home hospice, hospital palliative care units, or residential hospice. They often also delay their emotional transition to acceptance of mortality and may be unable to focus on end-of-life goals until very close to death. It is important for patients like M.K., irrespective of the prognosis, to have access to appropriate supports in an ambulatory setting, a palliative approach to care both from their primary care provider(s) and oncology team(s), and palliative medicine specialist support when needed. This is also true for patients living with non-cancer illnesses, and their relevant specialist care providers, especially in conditions where interventions such as organ transplantation can convert a rapid downhill trajectory to rehabilitation and survivorship almost overnight.

The use of methadone for analgesic purposes has been a relatively recent addition to the palliative care toolkit and is still an intervention about which many physicians feel apprehensive. It can, however, be highly effective in patients who do not do well with other opioids, and is a vital part of the toolkit of physicians treating patients with chronic pain that is opioid-sensitive.

With respect to access to methadone for analgesia, it is useful to review its history.[1] Methadone was synthesized in Germany in the late 1930s. Methadone's pharmacologic properties were not initially well understood, and it was not seen as particularly useful at the time. Commercial production in the United States was started in 1947. Its trade name became Dolophine™, derived from the French *dolor* (pain) and *fin* (end). Over the next 50 or so years, the excellent oral bioavailability of methadone and its slow clearance led to recognition of its potential to prevent opioid withdrawal with a single daily dose. Methadone established itself worldwide as the primary means of treating opioid use disorder.

In the 1980s, when methadone first started to be used for pain in palliative care, it was thought that it had the same potency (milligram for milligram) as morphine, based on single-dose studies in healthy volunteers. The error of this extrapolation to the chronic dosing context rapidly became clear, as many patients became obtunded with inappropriately large doses that were prescribed when switching from high doses of other opioids. This is the basis for the general nervousness that is still induced in many healthcare professionals when considering methadone for pain. In Canada, the federal Ministry of Health deemed methadone too dangerous to use without a special authorization. The process of acquiring an authorization was delegated to the provincial and territorial colleges of physicians, who instituted a variety of processes for granting these authorizations, with no clearly defined standard of practice.

In Canada, the requirement for college authorization was a major disincentive to physicians prescribing methadone and perpetuated the perception of methadone being too dangerous for physicians to prescribe without special training. This restriction was lifted in 2018. Each provincial/territorial college now sets their own rules for methadone prescribing, both for pain and for opioid use disorder. A free 1-hour online course which satisfies these requirements regarding analgesic use is available through Canadian Virtual Hospice at http://www.methadone4pain.ca.[2]

Physicians in many centres already prescribe methadone as a second- or third-line opioid, with widespread anecdotal appreciation of its effectiveness. There is also increasing recognition of the

role that methadone can play as an adjuvant analgesic and also as a first-line opioid in certain circumstances.

Question 2. Why might M.K. benefit from a trial of methadone?

Methadone's effectiveness is thought to be due to, at least in part, its antagonism of N-methyl-D-aspartate (NMDA) receptors, in addition to its agonist activity on opioid receptors. It also interacts with a wide selection of the known subtypes of opioid receptors and has effects on serotonin and norepinephrine (noradrenaline) receptors similar to serotonin–norepinephrine (noradrenaline) reuptake inhibitors (SNRIs). Methadone is transformed to inactive metabolites by the liver and eliminated via the bowel, with clinically irrelevant additional clearance via the kidneys. Loss of renal function has little to no impact on clearance, and methadone is not dialysed.[3]

Physicians have been increasingly recognizing the benefits of methadone as an analgesic in situations where other opioids are either ineffective or not tolerated. Common indications for methadone treatment include:

- Opioid tolerance.
- Neuropathic pain.
- Pain in renal failure.
- Inadequate analgesia from other opioids.
- Opioid-induced hyperalgesia.
- Opioid toxicity.[4]

M.K. has a number of reasons to benefit from a trial of methadone—he is showing evidence of opioid toxicity (myoclonus and possible early delirium); his pain has a neuropathic component (chemotherapy-induced peripheral neuropathy and probable thoracic radiculopathies from tumour invasion); he has renal impairment; and he has inadequate analgesia despite increasing opioid doses, which may signify opioid tolerance and/or hyperalgesia (see Chapters 3 and 4 on nociceptive pain and Chapter 5 on neuropathic pain). Even if M.K.'s increasing pain is due entirely to progressive cancer, he has reached dose-limiting side-effects from hydromorphone and needs to change to a different opioid.

Question 3. What methods might you consider when starting M.K. on methadone?

There are two aspects to this question—'How much?' and 'How often?'. Methadone's long half-life leads to a higher risk of accumulation and delayed respiratory depression than for other opioids, if inadvertently overdosed. Its relative potency can vary widely between individuals, so it can also be difficult to predict an equianalgesic dose of methadone when switching from another opioid. This pharmacokinetic profile has made some physicians justifiably wary of prescribing it. The safety concerns about methadone were based on cases where inappropriately high starting doses were used and/or when doses were escalated faster than would be sensible, given methadone's known pharmacokinetics. A 2018 study comparing two very fast-switching methods (stop–start and only 24 hours of overlap) reported a high (57%) switch failure rate, with 13% of the patients suffering a non-deliberate opioid overdose, some requiring naloxone therapy.[5] It is not surprising that this and other fast-switch studies report a high incidence of inadvertent respiratory depression or 'narcotization' and perpetuate the reputation of methadone being a dangerous drug. As

a consequence of these concerns, even since the lifting of prescribing restriction, many patients with severe pain are still denied access to methadone.

The pharmacological properties of methadone mandate that it would be safest started in low doses and escalated slowly. Instead of starting slowly, waiting until a patient is in a crisis and then switching to methadone in a rush is more likely to lead to inadvertent overdose. Starting with a small dose and increasing gradually once steady state can be expected to have been reached (i.e. after at least 3 days) is much safer, as it would allow for methadone to be initiated in outpatients, titrated to effect based on steady-state pharmacokinetics. This slow transition from another opioid to methadone is as effective as, and much safer than, a rapid switch via calculations based on current opioid use of equianalgesic ratios of dubious value.

Early prescribers of methadone generally used it as a last resort in palliative care units, when patients were in a pain crisis, often with severe opioid toxicity, and it was observed that the higher the dose of the prior opioid, the more careful they had to be with methadone dosing. Though there was a general trend to needing a higher dose for highly opioid-tolerant patients, there seemed little correlation between prior opioid and eventual methadone dose.[4,6] Graphs comparing morphine equivalent dosing (MEDD) before a switch and the eventual dose of methadone with a dot for each switched patient looked very much like random snowstorm pictures (see Figure 31.1)! This makes sense, as many patients on high-dose opioids have a degree of tolerance to the respiratory depressant effect of their current opioid. Methadone's opioid receptor agonist profile

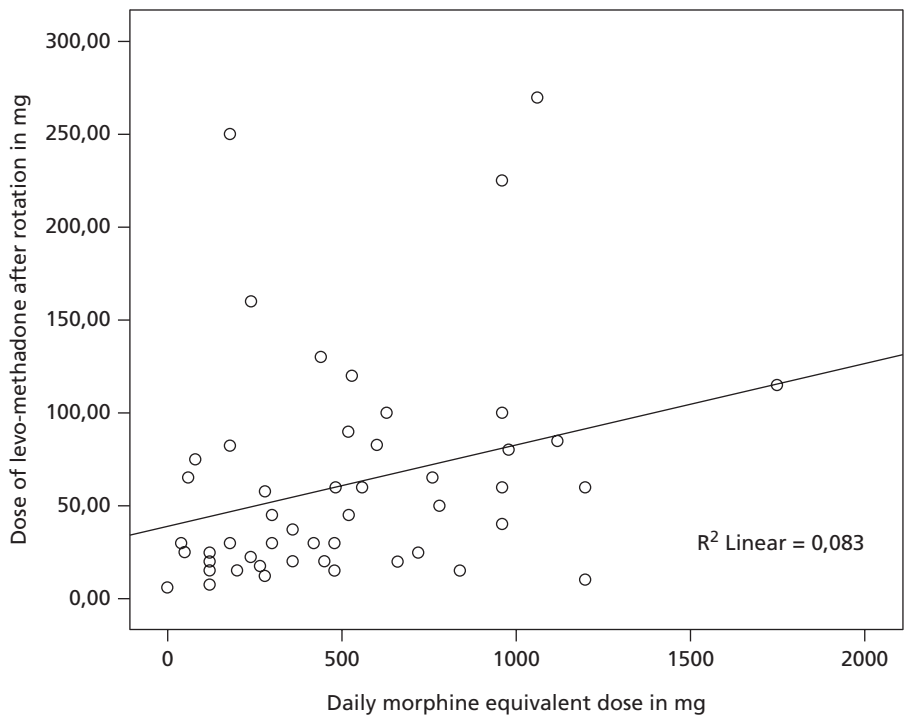


Fig. 31.1 Before and after switching equivalent doses of morphine and methadone.
Reproduced with permission from Ostgathe C, et al. 'Practicability, safety, and efficacy of a "German model" for opioid conversion to oral levo-methadone'. *Supp Care Cancer.* Vol. 20, Issue 9. pp. 2105–10. Copyright © 2012 Springer Nature.

Table 31.1 Methadone switching strategies

Approach	Level of urgency	Medical supervision
Stop and Go	High	24-hour experienced medical supervision (e.g. palliative care unit)
Stepped Switch	Medium	Varies from at home with nurse home visits and/or phone calls, with competent resident caregiver, to non-specialist inpatient care, depending on speed of switch
Start Low, Go Slow	Low	At home with outpatient clinic appointments and availability of telephone support if needed

may differ substantially from other opioids ('non-cross-tolerance'), with the patient not being as tolerant to methadone as they have become to other opioids. Patients on high-dose opioids often also have a degree of opioid-induced hyperalgesia. When the offending opioid and its metabolites are allowed to clear, hyperalgesia will usually resolve and pain will improve, thus lowering analgesic requirements.

Hyperalgesia and tolerance are not easily measurable but can be suspected clinically, based on history and physical examination, and are discussed in more detail in Chapter 2.

Switching to methadone

Clinicians around the world have responded to the unpredictability of methadone requirements with three kinds of approach, each of which suits a different degree of urgency and level of medical supervision. They can be organized into Stop and Go, Stepped Switch, and Start Low, Go Slow strategies (see Table 31.1).

These approaches have not been compared; indeed, it would be inappropriate to compare them head-to-head because each is most suitable for a different situation.

The safest method is Start Low, Go Slow.

Start Low, Go Slow

This method does not rely on any equianalgesic dose calculations other than a general awareness that those on high-dose opioid therapy may eventually need higher doses of methadone. This method is appropriate for patients who are experiencing inadequate analgesia but who do not display signs or symptoms suggestive of severe opioid toxicity (e.g. sedation, delirium).

The prior opioids (if any) are continued, including sustained-release preparations, and methadone is added in a small dose of 1 mg q8h. For those having previously demonstrated extreme opioid sensitivity, or who are very frail, an even smaller dose of 0.5 mg q8h may be appropriate. For those on large doses of opioid, 2 or 2.5 mg methadone q8h may be more appropriate. A therapeutic dose will be reached more quickly, but the larger the initial dose, the more closely the patient needs to be monitored.

1. Patients are instructed to wait at least 3 days, and then reassess their pain levels and consumption of their prior breakthrough opioid.
2. The next step is to increase the dose of methadone by 100% (i.e. doubling it) and to wait another 3 or more days to reassess the effect, continuing the increase with each step up being in multiples of the initial dose. If the 3-day interval is inconvenient, a longer interval can

be used that fits with availability of supervision such as weekly office visits or twice-weekly phone calls.

3. As soon as adequate analgesia is reached, the prior opioid should start being reduced, at a speed and increment size determined by the clinical situation and pharmacokinetics of the particular product being used. For example, transdermal fentanyl 100 mcg/hour could be reduced by 25 mcg/hour in four 3-day steps, or by 12 mcg/hour in eight 3-day steps. Long-acting morphine 90 mg q12h could be reduced every 24 hours in three steps of 30 mg, or six steps of 15 mg, depending on the clinical situation.
4. The dose of methadone will usually need to be increased as the prior opioid is cleared, and this can be done in the same fashion as previously, until all the prior opioid is gone and the final dose of methadone is stable.
5. If there is an incident pain component, a short-acting dose of a non-methadone opioid should always be made available throughout and after the switch, the selection of dose being based on the pre-switch MEDD dose, modified by observed effectiveness and side-effects.

Stepped methods

Stepped methods start with the premise that there is a degree of predictability of equianalgesic dosing between methadone and other opioids, but by doing the switch in a number of steps, there is a 'safety net' built in by providing regular opportunities for assessment in time to make adjustments to the target dose based on actual effect. The more urgent the situation, the smaller the number of steps and the larger the percentage of total MEDD the steps can be, but the higher the risk of inadvertent overdose. A stepped method is appropriate for patients who have some signs or symptoms of opioid toxicity but who are not in a pain crisis and have no other reason for hospitalization.

A number of experienced prescribers of methadone in palliative care settings have attempted to provide guidance on how to determine the equivalency in dose between methadone and other opioids, including Ripamonti (1998) , Ayonide (2000) , and Mercadante (2001) (see Table 31.2),[7] but these differ quite substantially because they assume the same equivalence ratio applied for broad, but different, ranges of MEDD, particularly at high doses. For example, an MEDD of 900 mg/day would be considered equivalent to 112 mg methadone/day according to Ripamonti; 45 mg according to Ayonide; and 75 mg according to Mercadante. An MEDD of 100 mg/day would convert to 17 mg methadone/day according to Ripamonti; 10 mg/day according to Ayonide; and 8 mg/day according to Mercadante.

The above ratios are obviously very roughly estimated, with a need to extrapolate the points in between the selected step-up dose points.

By smoothing out the end of range cut-off points, a continuous line can be drawn, which is more likely to be appropriate (see Figure 31.2).[1]

Table 31.2 Equianalgesic ratio comparison from different authors

MEDD (mg)	30–90	90–300	>300	600–800	800–1000	>1000
Ripamonti (1998)	4:1	6:1	8:1			
Ayonide (2000)	(<100) 3:1	(100–300) 5:1	(300–600) 10:1	12:1	15:1	20:1
Mercadante (2001)	4:1	8:1	12:1			

Source: data from Baumrucker S, et al. 'A new mathematical approach to methadone conversion. Journal of Pharmacology and Pharmacotherapeutics. Vol. 7, Issue 2, p.93. (2016) Medknow Publications and Media Pvt. Ltd.

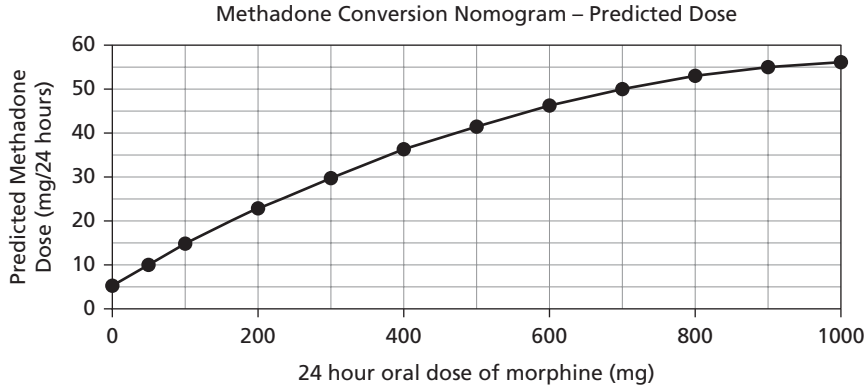


Fig. 31.2 Toombs conversion ratio chart.
Reproduced from Toombs JD. 'Oral Methadone Dosing for Chronic Pain: A Practitioner's Guide'. Pain Treatment Topics; Mar, 2008.

It should be clear, however, that this scientific-looking nomogram could mislead prescribers into thinking that an equianalgesic dose can be reliably predicted in any one individual. There is still marked variation between people, but it is as good a 'guesstimate' as anything else for where to start. The switching method is what is the most important, as therein lies the means of adjusting to the individual's needs, which may lie far from the line.[8,9]

Modified Edmonton method: a 3 x 3 day-stepped substitution

This method is quite aggressive, while still allowing for adequate time for steady state to be achieved between dose changes (see Table 31.3). It starts with calculation of the MEDD and then asks you to calculate an equivalent total dose of methadone per day, according to a guide such as the Ayonrinde table or the Toombs nomogram. The opioid is initially reduced by one-third and substituted by a third of the final total equivalent dose of methadone. The original Edmonton method suggested making the next dose change step in 24 hours, but if there is time, 3 days is safer, as it allows the methadone blood level to reach steady state and reduces the risk of delayed accumulation. Thus, after 3 days, the second third is substituted (i.e. the prior opioid dose halved and methadone doubled), and after a further 3 days, the last third of the substitution is completed. At each step, the methadone dose can be adjusted to allow for inter-individual variation in responsiveness, so that over- or under-dosing can be identified and the plan adjusted accordingly. It is quite common not to need all (sometimes any) of the last third of the methadone to be added because of greater effectiveness of methadone than predicted by the equianalgesic ratio chosen.

In Stepped Switch, it may be helpful to use short-acting preparations of the prior opioid once the first step is completed, for added ability to dose-adjust; however, for patients who do not have 24-hour nursing, the inconvenience of frequent dosing should be taken into consideration.

Table 31.3 Three-step switch ('modified Edmonton method')

<table>
<tr><th>Baseline</th><th>Days 1–3</th><th>Days 4–6</th><th>Days 7–10</th><th>Day 10 on</th></tr>
<tr><td rowspan="3">Prior opioid</td><td>Methadone</td><td rowspan="2">Methadone</td><td rowspan="3">Methadone</td><td rowspan="3">Fine-tuning</td></tr>
<tr><td>Prior opioid</td></tr>
<tr><td>Prior opioid</td></tr>
</table>

Table 31.4 Five-step switch

Baseline	Days 1–3	Days 4–6	Days 7–9	Days 10–12	Days 13–15	Day 15 on
Prior opioid	Methadone	Methadone	Methadone	Methadone	Methadone	Fine-tuning
	Prior opioid	Prior opioid	Prior opioid	Prior opioid		

If there is not too much urgency to complete the switch, more steps can be made, as in Table 31.4, showing a five-step switch.

Just as with the Start Low, Go Slow method, the step intervals can be extended to be convenient for the prescriber, for example weekly, to fit with outpatient clinic or family doctor office visits.

Stop and Go methods

Stop and Go methods are based on the fact that a large amount of methadone is required to saturate the body fat stores before it 'spills over' into the rest of the tissues where it provides analgesia. Rather than just allowing time for this to happen in a Start Low, Go Slow start or Stepped Switch, Stop and Go methods load up the patient with methadone very quickly and then back off once the patient is comfortable, to a maintenance dose. The prior opioid(s) is/are stopped and the patient given a fixed dose of methadone regularly, sometimes with additional doses as needed, until the patient achieves pain control, usually within 3 days. At this point, they add up the amount taken so far, and continue at a dose reduced by at least 50%, with further adjustments based on effectiveness and tolerability. Some methods use a fixed dose, irrespective of the prior opioid dose, and some select the dose based on an equianalgesic dose ratio. Clearly, the point at which analgesia can occur and the point at which overdose can occur can be very close, and this method is only safe to be used in a setting with experienced professionals and close nursing supervision such as a palliative care unit.

An example of a simple Stop and Go method that does not take prior opioid dosing into account is the German model:

1. Stop prior opioid(s). Start fixed dose of methadone 5 mg q4h plus q1h PRN, irrespective of prior opioid consumption.
2. Increase or decrease by 30% within first 72 hours, according to effect.
3. After 72 hours, the total 24-hour dose is halved and delivered, split into three doses a day, plus an additional dose q3h PRN.

A retrospective study of this method was described as having an 85% success rate and no naloxone infusions were needed in 52 German palliative care unit inpatients, with 98% with a primary diagnosis of cancer and 75% discharged alive.[10] The MEDD was calculated according to an accepted table (hydromorphone 5:1, fentanyl 100:1). Little to no correlation between prior MEDD and eventual methadone dose was seen.

The best-known Stop and Go method is the 'Morley and Makin method' which incorporates an equianalgesic conversion calculation (see above).

Morley and Makin method

(modified on palliativedrugs.com)[11]

1. Stop the prior opioid(s). Give a single dose of oral methadone which is 1/10th of the previous 2-hour MEDD dose, up to a maximum of 30 mg, followed by 1/30th of the prior 24-hour dose of MEDD, to a maximum of 10 mg 3-hourly as required.

2. On day 6, the amount of methadone taken over the previous 2 days is noted and divided by 4 to give a regular 12-hourly dose, with 1/4 of the regular 12-hourly dose allowable in addition q3h PRN.
3. If two doses or more per day of as-required methadone continue to be needed, the dose of regular methadone should be increased by 1/3 to 1/2 once a week.

As methadone has a long half-life, after several days of therapy, a dose reduction may be possible, without loss of analgesia, to reduce adverse effects such as drowsiness.[12]

This method has been widely used in palliative care units for patients in pain crises, and it is reported to be safe and effective in a care setting with highly competent nursing staff and round-the-clock physician supervision. Identification of the point at which pain control is reached and avoiding going on to overdose the patient require very close monitoring and this is not suitable for care settings that do not have such supervision.

Question 4. Which method do you think would be best for M.K.?

The level of urgency for M.K. is medium, in that he does not require hospitalization at this time (though he probably would need to be if he did not have such a capable wife to support him). A Stop and Go method would not be safe for him to do at home, and he does not want to come to hospital. A Start Low, Go Slow approach would be safe but may not respond to his needs fast enough. The possibility of delirium requires a reduction in his current opioid, so a stepped switch would be preferred.

1. Calculate the total daily opioid dose:

   His current total daily hydromorphone dose is 21 mg x 2 (42 mg), plus 4 mg x 3–4 (12–16 mg) = 54–58 mg/day.

2. Convert to MEDD:

   Using a 5:1 conversion ratio, this is equivalent to 270–290 mg/day MEDD.

3. Estimate the equianalgesic dose of methadone:

   The Ripamonti table suggests a 6:1 ratio, i.e. 45–48 mg/day.

   The Ayonrinde table suggests 5:1, i.e. 54–58 mg/day.

   The Mercadante table suggests 8:1, i.e. 34–36 mg.

   The Toombs nomogram suggests the final dose will be about 27 mg/day.

As you can see, this is not an exact science. The Toombs nomogram and Ayonrinde method fall in the extremes of the suggested range and halfway between them would be around 42 mg/day.

4. Decide how many steps you are going to take, each step being at least 3 days.

A three-step switch could be achieved in 9 days, which is fast enough to meet the need for rapid resolution of his opioid toxicity without taking too much risk of inadvertent methadone excess.

5. Divide the hydromorphone into 3 to suggest the reduction increment: 66 divided by 3 = 22 mg.
6. Decide how to make that reduction, given his use of long- and short-acting preparations.

There is more than one way to do this, as appropriate for the clinical situation. To reduce by approximately 22 mg/day, the 12-hourly Hydromorph Contin could be dropped by 12 mg (the closest possible increment to 11 mg, given the strengths available), that is to 9 mg q12h, with no change in breakthrough, OR the long-acting and breakthrough doses could be reduced in tandem, for example to 15 mg q12h plus 4–6 mg for breakthrough (rounding to the closest available strengths).

As M.K. has significant incident pain, is relatively comfortable overnight, and likes to be able to control his dosing, it makes sense to reduce the long-acting first. If he had primarily continuous pain, then reducing both preparations in tandem would be more appropriate.

7. Decide on your methadone dosing steps:

   42 mg/day divided by 3 is 14 mg. The first step would therefore be 14 mg/day, that is 4.7 mg q8h, which would be rounded up to 5 mg.
8. After 3 days, providing pain control is improving and M.K. is tolerating the methadone well, the methadone should be increased to 10 mg q8h and the hydromorphone dropped by another 22 mg/day, that is the long-acting could be discontinued altogether and the breakthrough left as is, or the long-acting could be reduced to 6 mg q12h. The remainder of the reduction should be accomplished by decreased use of breakthrough as the pain improves.
9. After a further 3 days, any long-acting hydromorphone should be stopped and the use of breakthrough assessed. The final increase in methadone up to 15 mg q8h can be made, and subsequently adjusted according to effect, with 3 days between any adjustments if possible.

Question 5. How would you write your prescriptions?

If your jurisdiction requires the use of a controlled drug prescription pad, ensure you complete it correctly and that a copy is kept in the patient's chart. Specify the strength of the solution (usually 10 mg/ml) or the strength of tablets (usually 1 mg to start with, or half of 5 mg if a high eventual dose is anticipated), and include specific instructions for doses and increases. Specify 'FOR PAIN' to avoid any confusion with use for opioid use disorder. A three-step switch will not be able to be adequately described on a prescription pad or conveyed legibly in entirety on a medicine bottle label, so make sure a separate schedule is written clearly and in detail for all to follow, and make sure that the patient and caregiver can explain it back to you to confirm understanding.

Question 6. What else do you need to do when initiating methadone?

When initiating methadone, it is important to inform all who need to be aware (i.e. family doctor, other specialists, home care programme) of the plan. Providing written instructions to the patient and caregiver is a vital step in ensuring the plan is followed correctly. If liquid methadone solution is to be used, a demonstration of how to measure it with a syringe is a very useful practical safety step. Using tablets may be safer and easier for patients with limited dexterity or cognitive limitations, but using different-strength tablets can sometimes be confusing. A compromise on dosing to make it possible to achieve the intended size steps using a single strength of tablets may outweigh a small increase in risk of under- or overdosing.

As with many new interventions with a degree of complexity, it is important to ensure that the patient and caregiver have someone to contact in the event of any need for reassurance or clarification of your instructions, and use any in-person observation methods at your disposal such as persuading M.K. to allow a home care nurse in just for medication supervision. Ensure that the home care nurse has clear instructions on who to call in the event that advice is needed, and provide the caregiver with a 24/7 contact number to call if necessary.

Question 7. What about side-effects?

Methadone has the potential to cause all of the side-effects that are caused by other opioids, including:

- Somnolence/sedation.
- Respiratory depression.
- Constipation.
- Nausea.

These side-effects are, however, generally less than seen with other opioids, providing dosing is well supervised. The propensity of methadone to cause constipation is similar to that of transdermal fentanyl, which is less than that of other oral opioids. This difference can manifest as transient diarrhoea when switching rapidly to methadone from a more constipating opioid, especially if a regular laxative regimen is not reduced.

Methadone can also (rarely) cause:

- Depression.
- Hypoglycaemia.
- Rashes.
- Peripheral oedema.
- Pulmonary oedema.
- Pruritus.

True allergy to methadone is very rare. In patients who have extreme sensitivity (including anaphylaxis) to other opioids, a small dose of methadone given under supervised circumstances can establish if the patient may be able to tolerate methadone, as is often the case, and a very conservative Start Low, Go Slow initiation may allow patients with severe pain who have been unable to tolerate any other opioids to achieve good analgesia.

QT interval prolongation

Methadone can prolong the QT interval and increase the risk of the ventricular cardiac arrhythmia torsades de pointes. This is rarely a clinically significant issue by itself in analgesic methadone doses, but if the dose is high (over 120 mg/day being a conservative threshold for checking) or if other predisposing factors are also present, this risk may become clinically relevant and an electrocardiogram (ECG) should be done.[13]

Heart rate inversely relates to the QT interval, that is the faster the heart rate, the lower the QT interval. Modern ECG machines correct it for heart rate automatically (QTc = QT divided by the square root of the R-R interval).

In men below the age of 55 years, the normal range for the QTc interval is 350–430 ms. For women, the comparable value is 350–450 ms. Concern arises when the QTc interval is between 450 and 500 ms. When the QTc interval is greater than 500 ms, the patient is at an increased risk of developing torsades de pointes.

Common causes for QT prolongation include:

- Congenital long QT syndromes (suggested by a family history of sudden death).
- Electrolyte disturbance:
  - Hypomagnesaemia.
  - Hypokalaemia.
  - Hypocalcaemia.
- Concurrent therapy with other QT-prolonging drugs.

A full list of QT-prolonging drugs is beyond the scope of this chapter, but the most clinically relevant to be aware of include the following classes:

- Antidepressants (e.g. amitriptyline, imipramine, nortriptyline, desipramine, doxepin, maprotiline).
- Antipsychotics (e.g. haloperidol, pimozide, ziprasidone).

- Antibiotics (e.g. erythromycin, clarithromycin, chloroquine).
- Antimalarials.
- Antihistamines (loratadine).
- Antiarrhythmics (e.g. quinidine, amiodarone, propafenone, sotalol).

Question 8. Are there any other drug interactions you should be aware of?

Drugs which interact with methadone generally involve inducers or inhibitors of the cytochrome P450 (CYP) system—mainly CYP3A4 and, to a lesser extent, 1A2 and 2D6. Many other drugs are metabolized by these enzymes and compete for metabolism with methadone, although they do not necessarily induce or inhibit the enzymes. Note that some genetic polymorphisms can influence enzyme distribution. See Tables 31.5, 31.6, and 31.7 for a list of medications that can interact with methadone. They should be referred to whenever a new drug is started or when a drug which has been in chronic use is discontinued. These lists are not exhaustive, and new drugs appear all the time in specialist fields such as oncology. If unsure, check!

Inhibitors

The most clinically important interactions are with inhibitors of P450 CYP3A4, as these can significantly decrease clearance and thereby increase blood levels of methadone. Examples of those most commonly encountered include ketoconazole, fluconazole, ciprofloxacin, erythromycin, fluvoxamine (Luvox®), fluoxetine (Prozac®), and cimetidine. When patients already on methadone are initiated on a P450 3A4 inhibitor, careful observation is required and the methadone dose may need to be reduced. Use of an alternative drug that does not affect that particular enzyme system would obviously be preferred if a suitable choice is available. If a patient is already on one of these medications when methadone is started, and providing that the initiation is by a slow and/or closely supervised method, the dose of methadone would just be expected to be a little lower than if the patient was not on an inhibiting drug. However, if that interacting drug were to be discontinued, clearance of methadone would increase, blood levels would drop, and the patient could lose effective analgesia. This can be anticipated, and patients instructed to increase their dose accordingly, with breakthrough dosing of a short-acting opioid to bridge the gap. The magnitude of the interaction is not easy to predict, but a change of up to 30% in methadone dosing could potentially be required.

Inducers

These drugs will reduce methadone levels, for example rifampin/rifampicin, phenytoin (Dilantin®), phenobarbital, and carbamazepine. Just as when initiating methadone for a patient already on concurrent therapy with an inhibitor, so long as the methadone is titrated carefully according to effect, the methadone dose will settle out appropriate to the current rate of clearance, a higher dose than would be needed in the absence of the inducer. It is important to recognize that discontinuation of the inducing drug will lead to slowing of clearance and a potentially clinically significant rise in the blood level of methadone. Patients, caregivers, and other involved health professionals should be alerted to, and regularly reminded of, this and if the inducing drug is stopped, the dose of methadone should be lowered. Again, the magnitude of the interaction is impossible to predict, but dose reductions of 10–30% may be required.

Table 31.5 Drugs that can increase methadone levels

Drug name	Additional concerns/notes	Potential alternative(s)
Alarithromycin	QTc prolongation/ *torsade de pointes*	Azithromycin
Alcohol (acute ingestion)	Competition for CYP450 enzymes	Advise patients against
Combination		
Alprazolam	Fatalities reported with combination	Buspirone, lorazepam
Amiodarone	QTc prolongation/ *torsade de pointes*	
Cannabis	Common metabolism pathway	
Cimetidine		Ranitidine, rabeprazole
Ciprofloxacin		
Diazepam	Additive CNS depression	Buspirone, lorazepam
Diltiazem		Therapeutic monitoring
Erythromycin	QTc prolongation/ *torsade de pointes*	Azithromycin
Fluconazole	QTc prolongation/ *torsade de pointes*	Terbinafine/clotrimazole troche
Fluoxetine	Increased serotonin syndrome risk; QTc prolongation	Mirtazapine
Fluvoxamine	Increased serotonin syndrome risk; QTc prolongation	Mirtazapine
Grapefruit juice and fruit		Therapeutic monitoring
Heroin	Decreased methadone-free fraction	
Itraconazole	QTc prolongation/ *torsade de pointes*	Terbinafine
Ketoconazole	QTc prolongation/ *torsade de pointes*	Terbinafine
Metronidazole		Therapeutic monitoring
Moclobemide	Increased serotonin syndrome risk	Mirtazapine
Paroxetine	Increased serotonin syndrome risk; QTc prolongation	Mirtazapine
Quetiapine		Olanzapine
Quinidine	QTc prolongation/ *torsade de pointes*	
Sertraline	Increased serotonin syndrome risk; QTc prolongation	Mirtazapine
Sodium bicarbonate	Decreased renal elimination	Therapeutic monitoring
Topiramate	Alkalinization of urine may increase half-life of methadone	Levetiracetem
Verapamil		Therapeutic monitoring
Voriconazole	QTc prolongation/ *torsade de pointes*	Terbinafine

This table focuses on potentially significant drug interactions between methadone and commonly used medications, and is not an exhaustive resource.

Potential alternatives are listed for consideration. They should only be used if the overall drug profile is reviewed, including all other drugs the patient is taking.

Table 31.6 Drugs that can decrease methadone levels

Drug name	Additional concerns/notes	Possible alternative(s)
Alcohol (chronic ingestion)	Increased methadone metabolism	Advise patients against combination
Carbamazepine	Possible opiate withdrawal	Levetiracetem
Cocaine	Lowered methadone trough level	
Dexamethasone	Possible at doses of > 16 mg per day	Therapeutic monitoring
Nicotine/cigarette smoking	CYP1A2 inducer	
Phenobarbital	Possible opiate withdrawal	Levetiracetem
Phenytoin	Possible opiate withdrawal	Levetiracetem
Rifampin	Possible opiate withdrawal	May require increased methadone dose
Risperidone	Possible opiate withdrawal	Olanzapine
Spironolactone	Observed in cancer pain patients	Therapeutic monitoring
St John's wort	Increased metabolism and elimination	Mirtazapine
Vitamin C (> 2000 mg/day)	Increased renal elimination	

This table focuses on potentially significant drug interactions between methadone and commonly used medications, and is not an exhaustive resource.

Potential alternatives are listed for consideration. They should only be used if the overall drug profile is reviewed, including all other drugs the patient is taking.

Table 31.7 Drugs that can have an unpredictable interaction with methadone

Drug name	Additional concerns/notes	Possible alternative(s)
Amitriptyline	QTc prolongation/ *torsade de pointes*	Mirtazepine
Desipramine	QTc prolongation, increased desipramine levels	Mirtazepine
Dextromethorphan (DM)	Increased DM levels	Therapeutic monitoring
Duloxetine	Increased duloxetine and methadone levels	Theoretical, but avoid if possible
Nifedipine	Increased nifedipine levels	Therapeutic monitoring
Nortriptyline	QTc prolongation, increased serotonin syndrome risk	Mirtazepine
Tamoxifen	Decreased formation of highly potent active metabolites of tamoxifen	Aromatase inhibitor or alternative opioid
Tramadol	Possible opiate withdrawal	Avoid this combination if possible
Venlafaxine	Increased venlafaxine and methadone levels; QTc prolongation/ *torsade de pointes*	Mirtazapine

This table focuses on potentially significant drug interactions between methadone and commonly used medications, and is not an exhaustive resource.

Potential alternatives are listed for consideration. They should only be used if the overall drug profile is reviewed, including all other drugs the patient is taking.

Substrates

Substrates are drugs that compete for metabolism with methadone, for example imipramine (Tofranil®), nortriptyline (Aventyl®), and alprazolam (Xanax®). The magnitude of interaction with methadone metabolism is less likely to be clinically significant than with inducers or inhibitors. Patients should, however, be made aware that a reduction in dosing may need to be made if they experience increased side-effects after starting the competing drug.

Quinidine and amiodarone also inhibit P450 3A4, which may lead to increased methadone levels.

Patients with impaired liver function need to be monitored carefully and methadone doses may need to be reduced as liver function deteriorates. These patients require frequent reassessment.

Alcohol will potentiate the sedative and respiratory depressant effects of methadone. Chronic alcohol use will initially induce enzymes and tend to reduce methadone levels, but if liver function deteriorates due to chronic disease and/or alcohol abuse, methadone will tend to accumulate. It is recommended that alcohol be avoided by patients maintained on methadone for chronic pain.

Benzodiazepines and methadone have additive toxicity and, when used in combination, enhance respiratory depression and sedative effects. In particular, benzodiazepines with active metabolites and a long half-life (such as diazepam, which is also metabolized by P450 3A4) should be avoided. Patients using both methadone and a benzodiazepine require careful monitoring.

Case 31.1 (continued)

M.K. starts the three-step switch as described and within 2 days, he is using less breakthrough and sleeping better and has less myoclonus. By the time he gets to day 6, he has excellent pain control and is only using one breakthrough a day, for when he showers. A week after completing the switch, he drops the dose of methadone from 12 mg q8h to 10 mg q8h. He accepts ongoing visits from the nurse, who has been also helping him and his wife talk to their children and to make a legacy video for them. He deteriorates slowly over the next 2 months. Immunotherapy is discontinued because of side-effects and disease progression. He becomes bed-bound and sleeps a lot. He declines any further tests and wishes to stay at home, understanding he will most likely die soon.

Question 9. What could you do to maintain analgesia with methadone if M.K. loses the ability to swallow as he approaches end of life?

Parenteral methadone is available in some countries but is no longer commercially available in Canada. If necessary, it can be compounded by certain pharmacies; however, it is very rare to need this as the rectal or transmucosal routes are usually accessible and effective.

Methadone oral solution is bioavailable at about 86% orally and 76% rectally, at least in healthy volunteers. Despite slightly lower total bioavailability, rectal absorption of the oral solution is actually a little quicker than by the oral route, due to the relatively alkaline environment and large surface area of the rectum. Custom-made suppositories are less well absorbed and not recommended. When patients lose the oral route (including being nil by mouth for surgery), the usual oral dose can be administered rectally, without dose adjustment initially and then be modified according to effect, the expectation being that a small (approximately 10%) dose increase may be required.

Because methadone is lipophilic, it can be absorbed quite well via the buccal/sublingual route, but volumes need to be small. If large doses need to be administered, it is better to give small concentrated doses more frequently than to risk non-absorption of larger volumes given less frequently.

Methadone can be delivered transdermally using the vehicle Lipoderm®. A recipe has been developed by a group in Nanaimo, British Columbia, with 10% methadone (100 mg/ml) being able to be put into pre-filled syringes, applied with a glove to the inside of the arm or other thin-skinned area of the body, rubbed in well, and kept dry for an hour. The skin has to be intact to avoid unpredictably higher absorption.[14]

References

1. **Toombs JD** (2008) *Oral methadone dosing for chronic pain: a practitioner's guide*. The Pain Community. https://paincommunity.org/resource-category/downloads/articles-downloads/ (Originally published in Pain Treatment Topics [updated 3 December 2008] 2008. http://pain-topics.org/pdf/OralMethadoneDosing.pdf
2. **Canadian Virtual Hospice**. *Methadone for pain in palliative care*. http://www.methadone4pain.ca
3. **Dean M** (2004) Opioids in renal failure and dialysis patients. *J Pain Symptom*, **28**(5), 497–504.
4. **Bruera E**, **Pereira J**, **Watanabe S** *et al.* (1996) Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. *Cancer*, **78**(4), 852–7.
5. **Poulain P**, **Berieur MP**, **Lefki S** *et al.*; **EQUIMETH2 Study Group** (2016) Efficacy and safety of two methadone titration methods for the treatment of cancer-related pain. *J Pain Symptom Manage*, **52**(5), 626–36.e1. https://www.ncbi.nlm.nih.gov/pubmed/27693901
6. **Mercadante S**, **Caraceni A** (2011) Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review. *Palliat Med*, **25**(5), 504–15.
7. **Baumrucker S**, **Jbara M**, **Rogers R** (2016) A new mathematical approach to methadone conversion. *J Pharmacol Pharmacother*, **7**(2), 93. doi: 10.4103/0976-500X.184773
8. **Lawlor P**, **Turner K**, **Hanson J**, **Bruera E** (1998) Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. *Cancer*, **82**, 1167–73.
9. **Ripamonti C**, **Groff L**, **Brunelli C** *et al.* (1998) Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? *J Clin Oncol*, **16**, 3216–21.
10. **Ostgathe C**, **Voltz R**, **Van Aaaken A** *et al.* (2012) Practicability, safety, and efficacy of a 'German model' for opioid conversion to oral levo-methadone. *Support Care Cancer*, **20**(9), 2105–10.
11. **Royal Pharmaceutical Society**. palliativedrugs.com
12. **Morley JS**, **Makin MK** (1998) The use of methadone in cancer pain poorly responsive to other opioids. *Pain Rev*, **5**, 51–8.
13. **Fanoe S**, **Hvidt C**, **Ege**, **Jensen GB** (2007) Syncope and QT prolongation among patients treated with methadone for heroin dependence in the city of Copenhagen. *Heart*, **93**(9), 1051–5.
14. **Love R**, **Bourgeois K** (2014) Topical methadone: an alternative for pain control in end of life management. *J Palliat Med*, **17**(2), 128.

Chapter 32

Medical cannabis

Pippa Hawley and Vincent Maida

Attitude

To enable each learner to:

- Understand that plant-derived cannabis and medical cannabinoids have existing and emerging evidence-based therapeutic effects.
- Reflect on the distinction between recreational cannabis and medical cannabis.
- Consider the potential for cannabinoid therapies to improve the quality of life (QOL) of patients referred for palliative care.
- Recognize the potential for cannabis-based therapies for opioid-sparing and reduction in overall polypharmacy.

Skills

To enable each learner to:

- Recognize situations where medical cannabis or a prescribed cannabinoid may be appropriate.
- Formulate a management plan utilizing medical cannabis and cannabinoids, including route, dosing, and titration schedules.
- Recognize adverse effects of cannabis and cannabinoids.
- Demonstrate proficiency in navigating the legalized Canadian Medical Cannabis programme.
- Listen and respond appropriately to requests by patients for cannabinoid therapies.

Knowledge

To enable each learner to:

- Describe the endocannabinoid system in basic terms.
- Describe the pharmacological properties of cannabinoids and the 'entourage effect' of plant-derived cannabis.
- Describe the common side-effects and interactions of cannabinoid therapies.

Case 32.1

B.H. is a 34-year-old married electrician with a history of locally advanced colon cancer treated with a left hemicolectomy, followed by adjuvant chemotherapy which included oxaliplatin. The oxaliplatin caused painful peripheral neuropathy. The painful numbness and tingling in his hands and feet have worsened since his last treatment, but he feels it is now plateauing in intensity. He was a slim individual prior to his surgery and lost approximately 30 pounds throughout the course of his illness. He is having difficulty regaining

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weight. He is having difficulty sleeping and is tired during the day. He is justifiably anxious that the cancer might come back. He has mild persistent pain around his abdominal scars, for which he takes regular acetaminophen and occasional ibuprofen. He is worried about their effect on his liver and stomach. He wants to put on weight, to sleep better, and to take fewer pain pills, and asks you whether medical cannabis might be worth trying, as he has heard about it from friends and family members. He is otherwise well, with no history of cardiac disease or psychiatric disturbance.

Question 1. What do you need to know to be able to respond to B.H.'s request for guidance?

It is beneficial for clinicians to have a basic understanding of the history of cannabis use, physiology of effect, options for products and routes available, and evidence for indications.

History

The first records of use of cannabis for medical purposes came from China around 5000 years ago where extracts of the plant were used for relief of cramps and pain. Most ancient cultures had a documented role for cannabis in ceremonial and/or medical contexts.[1] A 2500-year-old mummy, discovered in 1993 in an underground burial chamber in Siberia, was found to have a pouch containing cannabis buried alongside her. Magnetic resonance imaging showed that she had metastatic breast cancer, leading to speculation that medical use of cannabis for cancer-related symptoms was likely.[2] Once widely used as medicine, prohibition of cannabis in the 1940s led to loss of familiarity with its properties among the medical profession. Cannabis is now re-emerging as a therapeutic tool, an alternative medicine, or alongside medicines that have been shown to have limited benefits and/or significant safety concerns, including opioids, tricyclics, anticonvulsants, hypnotics, and anxiolytics. In Canada, access to cannabis for medical purposes has been legal since 1999, and legal for recreational use since October 2018. Worldwide, only Uruguay has a similar system of legal access for both medical and recreational purposes. Other countries are watching Canada closely as they consider similar legislation.

Physiology

The endocannabinoid system uses a complex network of G-protein-coupled cannabinoid receptors widely distributed throughout the body.[3] The CB1 receptor is the primary subtype in the central nervous system, particularly those parts concerned with appetite, pain, and memory, and CB2 receptors are primarily found throughout the immune system, modulating inflammation and immune cell activity. The main endocannabinoids are anandamide and 2-arachidonoylglycerol (2-AG), and their interactions with the CB1 and CB2 receptors are complex. The background state of balance in state of activation and modulation of the system maintained by endocannabinoids varies between different individuals and is postulated to cause or contribute to some illnesses such as fibromyalgia, obesity, and schizophrenia. Other physiological substances also interact with the CB1 and CB2 receptors, and the endogenous cannabinoids can also interact with other kinds of receptors, such as TRPV1, also involved in pain processing.

Therapeutic use

The *Cannabis* plant (almost exclusively the *sativa* and *indica* strains*)* produces a large number of active phytochemicals. The relative amounts of each component in natural cannabis vary

enormously from one strain to another and are also affected by cultivation and harvesting techniques. The main pharmacologically active cannabinoids are tetra-hydro cannabinol (THC) and cannabidiol (CBD). THC is responsible for most of the psychoactive effects, via stimulation of CB1 receptors widely distributed throughout the nervous system, but has therapeutic effects in other organ systems as well. CBD modulates the psychoactive effects of THC and also has its own therapeutic effects. To complicate the situation further, the *Cannabis* plants produce hundreds of other substances known to have therapeutic potential, including a variety of terpenes and flavonoids, which are also responsible for the smell, taste, and colour of the products. The interaction between cannabinoid and non-cannabinoid molecules constitutes the 'entourage effect',[4] where plant-derived cannabis products have effects that differ from those of pure or synthetic THC and from pure CBD extracts.

The ubiquitous footprint of the endocannabinoid system, both extracellularly and intracellularly, within the body makes attempts at its manipulation for one goal prone to effects elsewhere in the body. For example, in 2008, a CB1 receptor antagonist developed for management of severe obesity was withdrawn after a brief period of approval from the European market after it was found to be strongly associated with severe psychiatric disturbances, nausea, and upper respiratory tract infections.

The balance between THC, CBD, and the entourage molecules is important in determining the therapeutic effects and side-effects of an individual medical cannabis product. Careful consideration of cannabinoid balance and dosing has the potential to impact multiple symptoms simultaneously. It is important therefore to understand that medical cannabis is not a single entity, rather a class of compounds with many different potentially pharmacologically active products and complex synergies between them. There is much yet to be discovered about how to best harness their potential.[5,6]

Cannabinoid options

The challenge clinicians face relates to finding the optimal combination of THC and CBD that yields the best balance between positive effects and side-effects.[7] THC generally displays a very narrow therapeutic index ('therapeutic window'), that is too little generates no significant results, but further dose escalation may lead to significant side-effects such as psychoactive phenomena, dizziness, and hypotension. The therapeutic window can vary greatly between individuals, most likely influenced by a combination of genetics and environmental influences, including prior exposure. THC-naïve patients (i.e. with no prior experience with recreational cannabis) tend to be more likely to initially experience THC-related psychological side-effects such as euphoria, dizziness, sedation, or confusion. However, these effects are dose-related and reversible and tend to abate with continued usage. CBD used in conjunction with THC will broaden THC's therapeutic index.

Patients looking for relief of symptoms or anti-inflammatory effects from a medicine generally do not tolerate psychoactive effects well, and 'getting high' is considered an adverse effect. Medical cannabis products therefore usually have a lower THC and higher CBD ratio than those developed for recreational use, where high THC levels are considered desirable. The details of the entourage molecules of products are not consistently provided, but the relative proportions of THC and CBD are required for all Canadian legal licensed producers' (LPs) products, whether sold for medicinal or recreational purposes.

Products

Two synthetic THC analogues have been studied in clinical trials and approved by Health Canada: nabilone (Cesamet®) and dronabinol (Marinol®). Dronabinol is no longer available in

Canada, but nabilone (Cesamet®) is frequently used as an adjunct to standard antiemetics for chemotherapy-induced nausea. It has a narrow therapeutic index and contains no CBD. A plant-derived buccal spray called nabiximols (Sativex®) has a 1:1 ratio of THC:CBD and includes some entourage molecules. Nabiximols has also been approved for management of severe cancer pain but is prohibitively expensive for most patients. Research carried out in the development of these products informs providers but should not be assumed to reflect the expected effects of other non-pharmacologically developed products accurately.[8] Much research remains to be done, but in the meantime, a myriad of cannabis-based products is widely available in Canada and consumed by many patients with a variety of conditions.

The majority of Canadians access cannabinoid therapy as either dried plant product or plant extracts, and consume them in a variety of ways, including smoking, vapourizing, oils taken buccally/sublingually or swallowed, edibles (capsules or in foods such as cookies or brownies), suppositories, or topically. Though there have been some studies of smoked cannabis with primarily THC and little to no CBD, essentially none of the most commonly used cannabis-based products available for purchase by Canadian cancer patients have yet been studied in randomized controlled trials.

Routes

(See Table 32.1.)[9]

Though smoking cannabis has not been found to be associated with an increased risk of lung cancer, inhalation of any product of combustion exposes the lungs to toxic substances, with potential for harm. Vapourization has been proposed as a safer way to inhale cannabinoids, but an as yet unidentified component of commonly used vapourization substances has recently been found to cause a severe respiratory distress syndrome, sometimes fatal. Any inhalational route of ingestion is therefore not recommended.

Swallowing cannabis extracts subjects the product to delayed absorption and the first-pass effect, reducing the potency and delaying the onset and resolution of effects. The oral route is therefore not recommended for dose-finding, as approximately 8 hours or more may be required between doses to ensure avoidance of inadvertent excessive dosing.

Buccal/sublingual administration of an alcohol-based tincture or oil-based extract is not quite as rapid in effect as inhalation but is faster than swallowed. Oil extracts are also widely available from LPs, accurately labelled, and in a variety of strains, with multiple options of the THC:CBD ratio. Though oil extracts are more expensive than dried plant products, they are much more affordable than nabiximols. Buccal/sublingual oils are therefore currently the optimal choice for patients considering a trial of medical cannabis for symptom management.

There is as yet little to no evidence available to guide those interested in suppositories and creams. There is a widespread misconception among medical cannabis users that cannabinoids delivered by the rectal route do not cause euphoria.

Indications

(See Table 32.2.)

Pain is the condition with the best evidence of benefit from medical cannabis, especially from nabiximols, which is approved by Health Canada for neuropathic pain and muscle spasm in multiple sclerosis and for severe cancer pain. Nabilone is approved for management of nausea and vomiting due to chemotherapy, but many cancer patients report a preference instead for plant-derived cannabis for their nausea and loss of appetite throughout treatment. Anxiety and sleep disturbances are additional sources of suffering for patients with advanced illness. The effects of

Table 32.1 Cannabis routes of administration

Smoking	Vapourization	Oral	Other routes
◆ Most common route of administration, but not recommended (joints, bongs, pipes, etc.) ◆ Combustion at 600–900°C, producing toxic by-products: tar, polycyclic aromatic hydrocarbons (PAH), carbon monoxide (CO), ammonia (NH_3) ◆ Chronic use associated with respiratory symptoms (bronchitis, cough, phlegm), but not lung cancer nor chronic obstructive pulmonary disease (if cannabis only) ◆ Patients may mix with tobacco, increasing respiratory/cancer risk ◆ 30–50% of cannabis is lost to 'side-stream' smoke	◆ Heats cannabis at 160–230°C ◆ Reduced CO, but not complete elimination of PAH demonstrated to date ◆ Vapourization produces significantly less harmful by-products versus smoking ◆ Decreased pulmonary symptoms reported, compared to smoking	◆ Oils, capsules, and other oral routes increasingly popular due to convenience and accuracy of dosing ◆ Edibles (brownies/cookies) may be more difficult to dose ◆ Juicing and cannabis teas do not allow for adequate decarboxylation of raw plant ◆ Nabiximols oromucosal spray is currently the only cannabis-based prescription that delivers standardized dosage of CBD/THC in a 1:1 ratio with extensive research ◆ Tinctures and lozenges intermediate onset with limited research	◆ Topicals ideal for localized symptoms (dermatological conditions, arthritis), with limited research evidence ◆ Suppositories possibly indicated for specific populations (cancer, gastrointestinal symptoms, young/elderly, etc.) with variable absorption. THC hemisuccinate may allow for best absorption, with limited research ◆ Recreational routes include 'shatter', 'dabs', and concentrates. Deliver very high doses of THC with high risk of euphoria, impairment, reinforcement, toxic psychosis, orthostatic hypotension. Inappropriate for medical application

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cannabis and cannabinoids on anxiety are mixed. Low doses can help anxiety, but anxiety can also be a side-effect of cannabinoids.[10] In 2019, a retrospective chart review of patients using medical cannabis reported reduced anxiety, as well as decreased utilization of benzodiazepines.[11] An American cancer care study in 2019 also reported reduced sleep disturbance among patients using medical cannabis. Preclinical studies monitoring electrocortical activity in a rat model have demonstrated that cannabis improves sleep architecture by modulating both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep phases. Cannabis extracts have also been reported to reduce paraneoplastic night sweats, which are a common problem in cancer.[12]

The benefit of a high-CBD extract produced in Colorado (Charlotte's Web) on severe treatment-resistant seizures was followed by widespread well-documented cases of children with seizure disorders benefiting from high-CBD oil extracts. A pharmaceutical industry-developed product has recently been approved for use in Dravet syndrome and Lennox–Gastaut syndrome, which is approved by the Food and Drug Administration (FDA). Many children in Canada take high-CBD oils for seizures, with variability in effectiveness and preferred product. Further research is required to determine the optimal mix of cannabinoids and entourage molecules, if there is one.[12]

Table 32.2 Levels of evidence for cannabis-based medicines in various conditions

Cannabis and nabiximols supporting evidence	
Level of evidence	**Benefits**
Conclusive or substantial evidence of efficacy	◆ Adult chronic pain treatment ◆ Multiple sclerosis spasticity symptoms ◆ Chemotherapy-induced nausea and vomiting ◆ Treatment of intractable seizures in Dravet and Lennox–Gastaut syndromes (CBD)
Moderate evidence of efficacy	◆ Improving outcomes in individuals with sleep disturbances associated with chronic pain, multiple sclerosis, fibromyalgia, and obstructive sleep apnoea syndrome ◆ Decreasing intraocular pressure in glaucoma
Limited evidence of efficacy	◆ Symptoms of dementia ◆ Symptoms of Parkinson's disease ◆ Positive and negative symptoms of schizophrenia ◆ Symptoms of post-traumatic stress disorder ◆ Appetite and decreasing weight loss associated with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) ◆ Multiple sclerosis spasticity (clinician-measured) ◆ Traumatic brain injury/intracranial haemorrhage-associated disability, mortality, and other outcomes ◆ Symptoms of anxiety in social anxiety disorders (CBD) ◆ Symptoms of Tourette syndrome
Limited evidence of inefficacy	◆ Depressive symptoms in chronic pain or multiple sclerosis patients
Insufficient evidence of efficacy or inefficacy	◆ Addiction abstinence ◆ Symptoms of irritable bowel syndrome ◆ Cancers, including glioma ◆ Cancer-associated anorexia, cachexia syndrome, and anorexia nervosa ◆ Symptoms of amyotrophic lateral sclerosis ◆ Chorea and some neuropsychiatric symptoms associated with Huntington disease ◆ Dystonia

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There are many other conditions which have been reported to benefit from cannabis-based therapies, including Parkinson's disease, arthritis, migraine, Tourette's syndrome, post-traumatic stress syndrome, Crohn's disease, and others. Some of these are primarily anecdotally reported, and some have small studies to support them, but the evidence base is currently weak. Those considering a trial of medical cannabis for an unapproved indication in any individual patient should make every effort to avoid any other concurrent changes in management and clearly document the outcome of the trial as objectively as possible. Participation in clinical trials is encouraged.

Cancer treatment

Though there have been many anecdotal reports of various cancers responding to a variety of cannabis-based products and some encouraging *in vitro* studies showing a suppressive or

apoptotic effect of THC on some cancer cell lines, substantial human clinical trials looking at potential disease control have not yet been able to be done because of worldwide regulatory barriers. Epidemiological studies have actually shown an association between high-dose recreational cannabis and germ cell cancers in males. Many cancer patients, however, report taking cannabis in a variety of forms, with or without conventional therapies, to help cure their cancer.[13] The consequences of this have not yet been explored in the literature, but harm has resulted from inappropriate self-medication with cannabis-based products taken without medical supervision, particularly in efforts to cure cancer, where users do not have a symptom against which to titrate the dose. A small retrospective study also showed potential for reduced response to immunomodulatory cancer therapies when taken along with medical cannabis, though this association needs further investigation.[14]

Case 32.1 (continued)

After discussing the potential that medical cannabis may be worthwhile exploring for management of B.H.'s sleep disturbance, pain, anxiety, and appetite, he asks you what you would suggest he takes.

Question 2. How would you respond?

As discussed earlier, assuming that he is unable to afford nabiximols and can afford to pay for a non-pharmaceutically derived product, ideally you could recommend he purchases a cannabis-infused oil, preferably with either an equal amount of THC and CBD (1:1 ratio) or a higher CBD content. Nabilone would be potentially covered if he has an extended health insurance policy where the product was covered, but as nabilone contains no CBD, it may be more poorly tolerated than a balanced product with the CBD reducing the unwanted side-effects of THC.

Dosing

(See Table 32.3.)

Table 32.3 Administration factors in cannabis delivery methods

Issue	Smoking/vapourization	Oral	Oromucosal	Topical
Onset (minutes)	5–10	60–180	15–45	Variable
Duration (hours)	2–4	6–8	6–8	Variable
Pros	Rapid action, advantage for acute or episodic symptoms (nausea/pain)	Less odour, convenient and discrete, advantage for chronic disease/ symptoms	Pharmaceutical form (nabiximols) available, with documented efficacy and safety	Less systemic effect, good for localized symptoms
Cons	Dexterity required, vapourizers may be expensive, and not all are portable	Titration challenges due to delayed onset	Expensive, spotty availability	Only local effects

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The use of cannabis and cannabinoid therapies is highly individualized and customized according to the patient's clinical profile, symptom severity, and prior experiences with recreational cannabis. As yet, there are no published dosage studies or validated dosing guidelines. Clinical experience with cannabinoid therapies has led to the dictum 'start low and go slow' with respect to titration scheduling. This is particularly important for THC. Starting with CBD products alone may not provide therapeutic benefit but is likely to be well tolerated. Botanically sourced THC and CBD should be started at no more than 2.5 mg, regardless of product format, and titrated up as tolerated and according to effect. Since nabilone is a much stronger cannabinoid receptor agonist than botanically sourced THC, its starting dose is recommended to be between 0.5 and 1 mg per day. Comprehensive follow-up with patients is essential to evaluate outcomes and to provide guidance on future titration strategies.

The maximum daily dosage for nabilone and nabiximols are 6 mg/day and 12 sprays/day, respectively. Although Health Canada does not quote the maximum daily dose of botanically sourced CBD, the range of dosing for Epidiolex® (CBD) is up to 20 mg/kg/day. Contrary to the greater potency of synthetic THC over plant-derived THC, plant-derived CBD (accompanied by entourage molecules) is substantially more potent than Epidiolex®, and expected maximum doses would be much lower, up to approximately 250 mg/day, and more likely to be limited by cost than by side-effects.

Depending on their pain and symptom profiles, patients may benefit from using creative combinations of cannabinoid therapies that may include using pharmaceutical cannabinoids (nabilone and/or nabiximols), together with botanically sourced cannabinoids. For instance, cannabis oils swallowed every 6–8 hours may control baseline pain and other symptoms, while buccal/sublingual administration of small amounts of oil extract may be useful for more rapid response when needed for pain or other intermittent symptom(s) without the need for inhalation.

Case 32.1 (continued)

B.H. asks you what side-effects to look out for.

Question 3. What are the main side-effects and contraindications to cannabis and cannabinoids?

Adverse effects

Side-effects from medical cannabis are frequent, but generally mild and rapidly reversible with reduction in dose or cessation of use.[13] They include dry mouth, tiredness, dizziness, increased appetite, and cardiovascular and psychoactive effects. Other effects can include impaired short-term memory, impaired motor coordination, altered judgement, and paranoia or psychosis at high doses. Patients, however, frequently report that side-effects are less severe than with other medicines they had previously been taking for the same indication (s).[13]

It is important to know that respiratory depression from cannabinoid overdose is rare, except in poisoning in children. There are no reported cases of death occurring in adults due to poisoning by cannabis or cannabinoids. The density of cannabinoid receptors in the brainstem is very low, in contrast to the distribution of opioid receptors. Inadvertent overdose is unpleasant, but not fatal, in adults, but can be serious in children.

Withdrawal symptoms can occur in heavy recreational use but are rarely a problem with controlled medical administration of cannabinoids.

The amount of cannabis normally used for medicinal purposes is not believed to cause any permanent cognitive impairment in adults, though long-term treatment in adolescents should be weighed carefully as they are more susceptible to these impairments (see contraindications below). Heavy consumption of recreational cannabis in adolescents and youth can lead to serious neuropsychiatric adverse effects. Heavy recreational use can also cause a form of cyclical vomiting, notably relieved by hot showers/baths. This is not expected to be a common problem with the lower doses generally used for symptom management, but clinicians should be alert to the potential for nausea and abdominal pain caused by high-dose cannabis use in cancer patients who may be taking it in an attempt to treat their cancer.

High-dose CBD appears to be very well tolerated, but there are some reports of reversible elevation in liver enzymes when CBD is taken in conjunction with some anticonvulsants—a common scenario in children with severe epilepsy. Liver enzymes should therefore be monitored periodically when high-dose CBD is being consumed.

Contraindications

As noted earlier, cannabis is not one single entity, and most of the potential adverse effects of cannabis-derived products relate to the THC content.

The possibility of vasodilatation from THC causing hypotension makes cannabis use contraindicated in the setting of unstable cardiac conditions such as arrhythmias and unstable angina or heart failure.

As THC can cause psychosis, the presence of delirium or psychosis contraindicates use of TCH-containing cannabis products, especially in youth, where there is potential for long-term effects on motivation and mental well-being. Cannabis use has not been found in epidemiological studies to be associated with an increase in prevalence of schizophrenia but can trigger psychosis. A family history of schizophrenia is therefore also a contraindication to use of THC for symptom management.

It should be noted that CBD appears to have potential as an antipsychotic, but suitable THC-free medical-grade preparations have only recently become available and there has not yet been sufficient research to recommend CBD for therapy in psychosis.

High-dose CBD has anti-inflammatory properties and possible immunosuppressive effects. It is therefore contraindicated in conditions where depression of the immune system would be undesirable. This includes using concurrently with immune therapies for cancer such as nivolumab.

Drug interactions

Drug interactions caused by cannabis-based products depend on the chemical components/profiles of the cannabis preparations used. Clinically significant drug interactions with THC and CBD are thought to be rare, but there is potential for interaction with drugs metabolized by the same pathways, particularly cytochrome P450 3A4. Clobazam metabolism is significantly slowed by high-dose CBD, and both are often used in childhood epilepsy, with clinically significant consequences. If using the two medicines concurrently, the dose of clobazam should be reduced and the patient monitored for potential toxicity. CYP3A4 inducers (e.g. rifampin) may increase THC and CBD clearance, and inhibitors (e.g. ketoconazole) can reduce it. By making sure THC and CBD are initiated with the start low, go slow approach, patients will adjust their doses of medical cannabis appropriately and safely.[15] High-dose CBD has only been available for a short period of time, and clinically significant drug interactions may emerge over time with more widespread use.

Case 32.1 (continued)

B.H. asks, 'Do I have to stop driving if I take this?'

Question 4. Are there any concerns about medical cannabis use and driving?

The ability to drive vehicles or to operate machinery has been shown to be impaired by THC, at least until tolerance is developed, and occupational regulatory barriers may prohibit the use of cannabis-based medicines in certain situations. Just as for all medications with potential for cognitive impairment (including gabapentin, anxiolytics, antidepressants, opioids, etc.), patients should be advised not to drive if they feel in any way impaired by cannabis, whether for medical or recreational use.

Case 32.1 (continued)

B.H. asks, 'Where should I go to get the right kind of cannabis oil?'

Question 5. How does medical access to the cannabis system work in Canada?

Unless prescribing nabilone or nabiximols, in which case you would use a regular prescription, you would recommend that he explores the medical cannabis access system through the Health Canada website's list of LPs.[16] Filtering the list for 'Oil' will reduce the number of producers to look at. He should select the companies that sell suitable products and compare between them, bearing in mind that they should indicate stock is available. Once he has selected his preferred source, he has to register and download a 'Medical Authorization' form for his physician or nurse practitioner to complete and send in to the selected provider directly. There is no such thing as a prescription for the process. The Medical Authorization requires the name and contact information of the healthcare professional and also asks for a recommended maximum amount. Five grams of fresh cannabis is determined to be equivalent to 1 g of dried cannabis, and the quantity of products that is equivalent to a given quantity of dried marijuana is calculated by taking into account the weight of fresh or dried cannabis that was used to make the products. For the majority of first-time users, 'up to a maximum of 1 g/day in equivalent dried product' is sufficient, but sometimes higher doses of up to 'equivalent of 3 g/day' are required. Requests for higher dose authorizations should trigger discussion about how they are using the product, either to advise them on a more efficient extraction method (e.g. making tea out of dried plant product makes very little cannabinoids available for absorption), use for recreational purposes rather than medical, or the possibility of diversion. Sometimes, however, patients take high doses of CBD for legitimate medical purposes.

Once the LP receives the patient's registration and the Medical Authorization, they *may* contact the medical authorizer to confirm the authorization, and then the patient may purchase whatever product they choose. This is why it is important for the patient to be carefully instructed as to what to buy.

It should be noted that this process is quite complex, can take time to negotiate, and is a barrier to access for those without Internet access, a credit card, an address, or limited computer skills. Some patients are also reluctant to have their name recorded on any 'register', for fear of not being allowed to enter the United States. Actual use of cannabis by cancer patients far exceeds the number who use the Health Canada-approved system.[17]

Case 32.1 (continued)

B.H. asks, 'How much will it cost?'

Question 6. How do patients pay for medical cannabis?

Costs of medical cannabis

In Canada, oils are more expensive than dried plant product, and prices vary from $50CAD per bottle up to $150+CAD, depending on the strength, composition of the extract, and other factors such as if it is organic. Increasing competition and production are lowering prices. Receipts for products from LPs can be claimed as medical expenses on end-of-year tax returns, which may be an important consideration when patients are sourcing products. Very few extended health policies cover medical cannabis. Unlicensed dispensaries and other unregulated sources are often substantially cheaper, but the accuracy of labelling and absence of moulds, pesticides, and other contaminants are not assured with these, and they are thus not recommended.

Case 32.1 (continued)

B.H. finds the cannabis oil helpful and returns to work after another month, taking the cannabis oil only in the evening and on weekends. At one follow-up visit, he confides to you that he has been letting his father use some of his cannabis oil on an open wound on his ear which had not been healing well after surgery, with good effect. He asks you if this is OK to continue to do.

Question 7. Is there a rationale for topical use of cannabis extracts?

Topical use of cannabinoids

There are many issues worthy of discussion in this situation, but confining this to the therapeutic question only, there is emerging evidence that topical cannabinoids may have a useful role in wound management. Patients with advanced illness experience a high prevalence of integumentary wounds involving both cutaneous membranes and mucous membranes. The most common wound types include malignant wounds and pressure injuries, as well as wounds derived from vasculopathic and/or vasculitic aetiologies. The preclinical literature is reporting opportunities for use of cannabis-based medicines, composed of combinations of cannabinoids and non-cannabinoids, applied topically to wound beds and periwound tissues. Although wound healing is always the prime objective of wound management, wound palliation (palliative wound care or wound-related pain and symptom management) is equally important. Although controlled studies involving topical cannabis-based medicines (TCBMs) are yet to be published, a number of

publications have already reported positive outcomes when employing TCBMs in human subjects with otherwise complex and recalcitrant wounds. In 2016, a case report described pain relief and tumour regression in a patient with advanced squamous cell carcinoma. In 2017, a case series of patients with pyoderma gangrenosum reported both clinically significant analgesia and opioid-sparing effects.[18]

Conclusion

We are only at the early stages of fully understanding the therapeutic potential of manipulation of the endocannabinoid system, but keeping the following key points in mind will allow all healthcare professionals to feel confident in approaching patients in a supportive and logical manner.

- A comprehensive assessment of any patient with a chronic illness includes asking whether they have found cannabis or cannabis-based medicines to be helpful.
- There is evidence that use of cannabis-based medicines can provide symptom relief in a variety of conditions, especially in neuropathic pain and chemotherapy-induced nausea and vomiting.
- There are multiple routes of administration for medical cannabis, and the oral transmucosal route is optimal for most situations.
- Cannabinoid dosing depends on prior patient experience and underlying endocannabinoid tone; there are no standard doses.
- Always 'start low and go slow'!
- Cost and regulatory complexities represent significant barriers to access to medical cannabis for patients with chronic illnesses, including children.
- Healthcare professionals should be sufficiently informed about medical cannabis to be able to discuss the topic with their patients, without stigmatization.
- High-dose THC should be avoided, especially in those at risk of psychosis or delirium.
- As with any substance that can affect cognition, THC can cause adverse effects such as motor vehicle accidents; thus, patients should be educated about how to use cannabinoid-based medicine safely.
- There are still significant regulatory and funding barriers which discourage medical research into cannabis-based medicine—healthcare professionals caring for patients who take medical cannabis should actively participate in research whenever possible.

References

1. **Ren M**, **Tang Z**, **Wu X** *et al.* (2019) The origins of cannabis smoking: chemical residue evidence from the first millennium BCE in the Pamirs. *Sci Adv*, **5**(6). doi:10.1126/sciadv.aaw1391
2. **Liesowska A** (2014) Iconic 2,500 year old Siberian princess 'died from breast cancer', reveals MRI scan. *The Siberian Times*. http://siberiantimes.com/science/casestudy/features/iconic-2500-year-old-siberian-princess-died-from-breast-cancer-reveals-unique-mri-scan/
3. **Tóth KF**, **Ádám D**, **Bíró T**, **Oláh A** (2019) Cannabinoid signaling in the skin: therapeutic potential of the 'c(ut)annabinoid' system. *Molecules*, **24**(5), 918. doi:10.3390/molecules24050918
4. **Russo EB** (2019) The case for the entourage effect and conventional breeding of clinical cannabis: No 'Strain,' no gain. *Front Plant Sci*, **9**, 1969. doi:10.3389/fpls.2018.01969
5. **Abrams DI** (2016) Integrating cannabis into clinical cancer care. *Curr Oncol*, **23**, S8–14. doi:10.3747/co.23.3099

6. **Maida V**, **Daeninck PJ** (2016) A user's guide to cannabinoid therapies in oncology. *Curr Oncol*, **23**(6), 398–406. doi:10.3747/co.23.3487
7. **Casarett DJ**, **Beliveau JN**, **Arbus MS** (2019) Benefit of tetrahydrocannabinol versus cannabidiol for common palliative care symptoms. *J Palliat Med*, doi:10.1089/jpm.2018.0658
8. **Russo EB** (1969) The case for the entourage effect and conventional breeding of clinical cannabis: no 'strain,' no gain. *Front Plant Sci*, **9**, 1969. doi:10.3389/fpls.2018.01969
9. **MacCallum CA**, **Russo EB** (2018) Practical considerations in medical cannabis administration and dosing. *Eur J Intern Med*, **49**, 12–19. doi:10.1016/j.ejim.2018.01.004
10. Black N, Stockings E, Campbell G, Tran LT, Zagic D, Hall WD, Farrell M, Degenhardt L. (2019). Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. *Lancet Psychiatry*, **6**(12), 995–1010. doi: 10.1016/S2215-0366(19)30401-8. Epub 2019 Oct 28. Erratum in: *Lancet Psychiatry*, 2020 Jan;7(1):e3. PMID: 31672337; PMCID: PMC6949116.
11. **Purcell C**, **Davis A**, **Moolman N**, **Taylor SM** (2019) Reduction of benzodiazepine use in patients prescribed medical cannabis. *Cannabis Cannabinoid Res*, **4**(3), 214–18. doi:10.1089/can.2018.0020
12. **Carr C**, **Vertelney H**, **Fronk J**, **Trieu S** (2019) Dronabinol for the treatment of paraneoplastic night sweats in cancer patients: a report of five cases. *J Palliat Med*, **22**(10), 1221–3. doi:10.1089/jpm.2018.0551
13. **Hawley P**, **Gobbo M** (2019) Cannabis use in cancer: a survey of the current state at BC Cancer before recreational legalization in Canada. *Curr Oncol*, **26**(4), e425–32. doi:10.3747/co.26.4743
14. **Taha T**, **Meiri D**, **Talhamy S**, **Wollner M**, **Peer A**, **Bar-Sela G** (2019) Cannabis impacts tumor response rate to nivolumab in patients with advanced malignancies. *Oncologist*, **24**(4), 549–54. doi:10.1634/theoncologist.2018-0383
15. **Alsherbiny MA**, **Li CG** (2019) Medicinal cannabis—potential drug interactions. *Medicines*, **6**(1):3. doi:10.3390/medicines6010003
16. **Health Canada** (2019) *Licensed cultivators, processors and sellers of cannabis under the Cannabis Act*. The Government of Canada. https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/industry-licensees-applicants/licensed-cultivators-processors-sellers.html#a1
17. **STATCAN** (2019) *National Cannabis Survey, first quarter 2019*. Statistics Canada. https://www150.statcan.gc.ca/n1/daily-quotidien/190502/dq190502a-eng.htm
18. **Maida V**, **Corban J** (2017) Topical medical cannabis: a new treatment for wound pain—three cases of pyoderma gangrenosum. *J Pain Symptom Manage*, **54**(5), 732–6. doi:10.1016/j.jpainsymman.2017.06.005

Chapter 33

Interventional analgesic techniques

Philip Chan and Kelly Shinkaruk

Attitude

To enable each learner to:

- Recognize the potential roles of interventional pain medicine in relieving cancer pain.

Skills

To enable each learner to:

- Discuss the potential benefits and risks of coeliac plexus neurolysis (CPN) in the treatment of pain related to pancreatic cancer.
- Discuss the potential benefits and risks of neuraxial analgesia in the treatment of cancer pain.
- Discuss the advantages and disadvantages of an implantable intrathecal pain pump in the management of intractable cancer pain.

Knowledge

To enable each learner to:

- Summarize the multiple aetiologies of pain symptoms related to visceral tumours.
- Understand the mechanism of action of CPN in providing pain relief in the setting of upper gastrointestinal malignancies.
- Discuss the evidence of efficacy of coeliac plexus blocks in pancreatic cancer.
- Understand the mechanism of action of neuraxial opioids.
- Formulate a plan to transition a patient on oral or parenteral opioids to neuraxial opioids.

Case 33.1

J.L. is a 62-year-old woman who presented to her family physician with jaundice and upper abdominal discomfort radiating to the mid back. The patient was found to have a tumour in the pancreatic head that demonstrated wide local invasion on computed tomography (CT) scan. She was urgently seen by a hepatobiliary surgeon, who arranged for an upper endoscopy and simultaneous symptom management with biliary duct stenting. The jaundice resolved within a few days, but the tumour was determined to be unresectable. Despite 2 months of maximal medical management, including radiation and analgesics, J.L. continued to experience abdominal discomfort rated as 6/10 at rest, with elevation to 8/10 with meals and other activity, and her quality of life was significantly affected. The pattern of pain distribution is consistent with pancreatic visceral pain.

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Question 1. What are the underlying mechanisms responsible for J.L.'s pain symptoms and are there any anatomical structures that can be targeted for interventional analgesia?

In the setting of visceral tumours, pain symptoms are related to a combination of stretching or distension of the organ capsule, pressure on surrounding neural structures, ischaemia due to tumour invasion or compression of the blood supply, and inflammatory changes.[1] With upper abdominal malignancies, such as pancreatic cancer, afferent and efferent nerve transmission occurs through the coeliac plexus. The coeliac plexus is a network of ganglia that supply autonomic output to, and receive nociceptive input from, the distal stomach, liver, gall bladder, pancreas, spleen, adrenal glands, kidneys, small intestines, and the large intestine up to the mid-transverse colon. The coeliac plexus is a retroperitoneal structure located anterior to the T12 and L1 vertebrae, surrounding the abdominal aorta. Given its location and role in nociception from the pancreas, the coeliac plexus is a structure that can be targeted for analgesia in this patient population.

Question 2. How is coeliac plexus blockade achieved and what are common side-effects of the procedure?

The terms coeliac plexus block (CPB) and coeliac plexus neurolysis (CPN) are often used interchangeably; however, the medications used and the expected duration of action differ between the two. CPB is performed using a mixture containing a corticosteroid and a local anaesthetic, but the duration of effect is often limited and thus is not utilized in palliative care. CPN, which involves the injection of a neurolytic agent, either phenol or ethyl alcohol, around the coeliac plexus, can produce a longer response. Both agents cause Wallerian degeneration of nerve axons distal to the site of lysis; this disrupts the nerve cell transmission of pain and results in a nociceptive block. However, the nerve axons regenerate, and thus CPN usually provides 3–6 months of pain relief.[2] In many circumstances, this will provide an ample duration of analgesia in patients with a late diagnosis. A repeat procedure may be performed in this patient population.[3]

Blockade of the coeliac plexus can be achieved using a variety of techniques, approaches, and image guidance modalities; most commonly, the intervention is performed under CT guidance and, more recently, using endoscopic ultrasound (EUS) techniques. The description of the specific techniques is beyond the scope of this chapter, but the performance of CPB or CPN requires skilled operators and therefore, referral to an interventional radiologist or a pain medicine specialist, or a gastroenterologist with an interest in EUS, will be required to complete this procedure.

Common side-effects from both CPN and CPB include diarrhoea and orthostatic hypotension. These side-effects are transient, generally resolve within a few hours to days, and may be mitigated by providing the patient with an intravenous fluid bolus prior to the procedure. More serious side-effects include retroperitoneal abscess; haematuria if an externally placed needle traverses a kidney; pneumothorax as the coeliac plexus is close to the diaphragm; local anaesthetic toxicity if an intravascular injection occurs; and rarely damage to the aorta, paralysis, or nerve root damage.[4] Serious complications occur in approximately 2% of patients.[5]

Question 3. What is the evidence for the efficacy of coeliac plexus neurolysis in pancreatic cancer?

The use of CPN for pancreatic cancer has been studied extensively. The following provides a summary of evidence related to CPN in pancreatic cancer.

Does it reduce pain? Does it eliminate the need for opioids? Does it affect quality of life or survival?

A recent systematic review showed that CPN was associated with a statistically significant improvement in pain control, compared with standard treatment, but the reduction was small—6% reduction in mean visual analogue score (VAS), compared with baseline. There was a significant decrease in opioid usage and constipation, but there was no benefit with regard to other opioid-related adverse effects such as nausea, vomiting, and sedation. There was also no effect on health-related quality of life or survival. CPN does not eliminate the requirement for opioids, as most patients still require opioids to control pain until death.[6]

The reason CPN is not completely effective in relieving pain associated with upper abdominal malignancies is that the pain often involves multiple mechanisms, such as spread to the lymph nodes, musculoskeletal system, and abdominal wall or the peritoneum,[7] not solely transmission through the coeliac plexus.

What is the optimal timing for performing CPN?

Often, invasive procedures are only considered after the failure of medical therapy, 'as a last resort' when all else has failed. It has been theorized that CPN may offer a survival advantage if performed earlier in the disease state, by decreasing adverse events such as nausea and vomiting and by preserving immune function through a reduction in opioid usage and also potentially improved gastric motility due to unopposed parasympathetic activity after sympathetic denervation.[8] However, studies are inconclusive; one study did not show a significant difference in reduction in pain, opioid consumption, or quality of life with CPN done 'early' in the disease state (as characterized by low opioid requirements), compared to 'late' in the disease state (as characterized by high opioid requirements).[9] Another study suggests that EUS-guided CPN at the time of diagnosis of inoperable cancer results in better pain control at 3 months and a trend towards lower opioid consumption and improved survival.[10]

Does the location and extent of spread of the pancreatic tumour affect the efficacy of CPN?

One study demonstrated that sustained and effective pain relief occurred in 92% of patients with cancer of the head of the pancreas, but in only 29% of patients with cancer of the body and tail of the pancreas. The reason for this difference is not clear, but in this study, cancer of the body and tail of the pancreas demonstrated more advanced tumour infiltration and metastatic spread at diagnosis; the involvement of multiple pain pathways (peritoneal, retroperitoneal, and somatic) may limit the benefits of CPB. Furthermore, in those patients for whom the procedure did not provide relief, there was extensive tumour growth around the coeliac plexus.[11]

Case 33.1 (continued)

J.L. undergoes EUS-guided coeliac plexus neurolysis and is able to reduce her opioid dose. After 2 months, she notices that the pain is returning and she is requiring increasing doses of opioids, which is starting to cause myoclonic jerks, sedation, and cognitive impairment. J.L. inquires whether there are any further analgesic options, given that the CPN has not lasted as long as hoped.

Question 4. Are there any other treatment options available to this patient?

In this situation, the patient may benefit from a neuraxial analgesic technique such as continuous epidural or intrathecal analgesia.

Question 5. How does neuraxial analgesia work?

In the 1970s, opioid receptors were identified in the spinal cord and shown to produce potent analgesia in animal models.[12] Opioid receptors in the spinal cord are concentrated in the grey matter of the spinal cord dorsal horn (primarily laminae II).[13] The mechanism of action of neuraxially administered opioids is not fully understood, but activation of mu opioid receptors located presynaptically on primary afferent neurons within the dorsal horn inhibits transmission of nociceptive stimuli from C and A-delta fibres.[14]

A brief introduction to the anatomy of the spinal cord and the surrounding elements is important in understanding the behaviour of different types of neuraxial opioids. The spinal cord grey matter is surrounded by a thin layer of white matter. Adherent to the white matter is the *pia mater*. Between the *arachnoid mater* and the pia mater is the sub-arachnoid space, which contains cerebrospinal fluid (CSF); medications delivered *intrathecally* are deposited into this space. A thin space containing a film of lymphatic fluid exists between the arachnoid mater and the outermost *dura mater*; the space outside of the dura is known as the *epidural space*. The epidural space contains a large amount of fat, as well as a prominent venous plexus.

One of the key factors to understanding the distribution of medications deposited in the epidural space or in the sub-arachnoid space is the concept of *hydrophilicity* or the affinity of a particular molecule for water.[15] It is useful to compare and contrast the behaviour of two commonly used neuraxial opioids—morphine, which is hydrophilic, and fentanyl, which is lipophilic (and thus hydrophobic).

Morphine deposited into the epidural space partitions out of the fat-filled space rapidly because of its hydrophilicity. It traverses the dura mater and the arachnoid mater and enters the CSF. Morphine persists in the CSF for a prolonged period, given its affinity for water. CSF circulation carries the morphine suspended in it towards the brainstem where it can cause side-effects such as respiratory depression. CSF circulation is slow, and the amount of morphine that reaches supraspinal sites depends on how much morphine is cleared out of the CSF into the spinal cord, or out into the systemic circulation, before it reaches the brainstem.

To get into the grey matter, morphine passes through the pia mater and enters the white matter. Morphine quickly traverses the white matter since it is approximately 80% lipid and thus represents a hydrophobic environment. Morphine persists in the grey matter because it is not heavily myelinated and is therefore more hydrophilic.

In contrast, fentanyl deposited into the epidural space quickly partitions into the epidural fat and eventually into the circulation because of its lipophilicity, and thus becomes unavailable for entry into the spinal cord. The systemically absorbed fentanyl can still reach supra-spinal sites where it could result in respiratory depression. Even if fentanyl is delivered into the sub-arachnoid space, it quickly partitions out of the CSF into the lipophilic environment of the white matter. From there, it is cleared into the plasma, and again very little reaches the active sites in the grey matter. This explains the clinical phenomenon that morphine is approximately 100 times less potent than fentanyl when given intravenously but is only four times less potent than fentanyl when given intrathecally.[16]

Question 6. Which medications are used for neuraxial analgesia?

Epidural infusions typically involve a mixture containing a local anaesthetic, such as bupivacaine, and an opioid such as fentanyl. Morphine can also be administered into the epidural space.

Health Canada has approved morphine for use in intrathecal drug delivery systems. In palliative medicine, morphine is the first-line medication for intrathecal infusion. If morphine is not providing adequate analgesia or is causing intolerable side-effects, consideration can be made for rotation to another opioid such as hydromorphone, fentanyl, or sufentanil; another type of medication, such as bupivacaine, can also be added to the opioid solution. These other medications are used in an 'off-label' indication. In other countries, a number of different classes of medications have been used, but these are not available for clinical use in Canada.

There is no consensus on the optimal method of converting the dose of systemic opioids to intrathecal opioids. Most published recommendations are based on anecdotal evidence and clinical experience. Some experts advocate starting at a standard dose of intrathecal morphine (1 or 2 mg per day), regardless of the dose of systemic opioids the patient is receiving, and titrating slowly upwards on the intrathecal dose while titrating downwards on the systemic dose. The downside to this approach is that it may take weeks to months to achieve a satisfactory intrathecal dose, during which the patient may continue to experience unremitting pain and potentially lose faith in the effectiveness of the therapy. Others employ conversion tables to determine an equivalent dose, and then titrate the intrathecal dose while titrating downwards on the systemic dose. The downside of this more aggressive approach is the potential for respiratory depression.[17]

Withdrawal symptoms can be observed as the systemic opioids are titrated downwards, because while intrathecal opioids activate spinal opioid receptors, supra-spinal and peripheral sites are no longer exposed to opioids, precipitating withdrawal symptoms.[18]

Side-effects of intrathecal opioids are similar to those associated with systemic administration: opioid-induced hyperalgesia, hypotension, sedation, respiratory depression, pruritus, hypogonadotrophic hypogonadism, urinary retention, and immunologic compromise.[19]

Question 7. What are the indications of, and contraindications to, neuraxial analgesia?

Neuraxial analgesia is considered when systemic opioids are not providing adequate analgesia and/or intolerable side-effects are encountered. Contraindications to neuraxial analgesia include patient refusal, elevated intracranial pressure, anatomical abnormalities (e.g. severe scoliosis, previous surgical instrumentation), tumour mass at the proposed catheter insertion site, allergy to the medications being used, haemodynamic instability, bleeding diathesis, active infection at the site of insertion or sepsis, and inexperience of the practitioner. A thorough discussion of the risks and benefits of the procedure need to be carried out in situations where contraindications may exist. For example, patients with coagulation abnormalities might consider insertion of a catheter despite the potential risk of spinal haematoma formation and paralysis. While this would not be acceptable in a non-cancer patient, a palliative patient may decide that improved analgesia at the end of life is of greater benefit than the potential risk of paralysis.

Question 8. What are the advantages and disadvantages of epidural versus intrathecal infusions?

Epidural catheters are inserted percutaneously near the spinal level corresponding to the innervation of the structure of interest (in this case, in the low thoracic region) and connected to an external pump system. Intrathecal catheters are inserted in the lumbar region (below the conus around L2) and connected to an external pump system or an implantable pump. When choosing

a technique, several considerations must be made, including the patient's life expectancy, the location and extent of pain, the goals of care and treatment, resources available, and the disposition.

The expertise and materials for initiation of epidural infusion are more readily available than for intrathecal infusion systems. Epidural infusion can provide focal analgesia, which may be useful in treating pain associated with chest wall tumour, for example. The downside of epidural infusions is that large volumes of medications are required (6–10 ml/hour are typical); the external pump and paraphernalia impede patient mobility, and there is an increased risk of infection.

Implantation of an intrathecal drug delivery system is often considered in treating diffuse pain. Typically, a programmable battery-powered pump, consisting of a motor and a reservoir, is surgically implanted under the skin in the anterior abdominal wall and connected to an intrathecal catheter. The main advantage is that the entire system is self-contained, with no external paraphernalia, potentially improving patient mobility, and does not carry the same risk of infection as an epidural catheter system. The pump typically delivers 0.25–0.5 ml of medication per day, and the reservoir holds enough medication to last anywhere from 3 to 6 months.

Question 9. When should an implantable pump be considered and how is it managed?

While an intrathecal drug delivery pump brings many advantages, it has a high upfront cost and the availability of clinical expertise and public funding for intrathecal pumps vary from province to province. Economic analysis suggests a 3-month life expectancy to be the approximate 'break-even' point for the implanted pump to become more cost-effective than the external system.[20] Modern-day pumps are programmable; using a dedicated clinician programmer, the delivered dose can be altered easily. Once implanted, the pump requires little in the way of daily care. The pump may need to be refilled every 3–6 months, which is a percutaneous procedure that can be carried out in an outpatient setting. Patients and their caregivers need to be educated on the warning signs of potentially life-threatening overdose or under-dose, signalling potential pump and/or catheter malfunction, and when and where to seek emergency care.

References

1. **Wordliczek J**, **Zajaczkowska R** (2013) Mechanisms in cancer pain. In: Hanna M, Zylicz Z (eds.) *Cancer Pain*, pp. 47–70. Springer, London.
2. **Pratt RB**, **Cousins MJ** (1998) Techniques for neurolytic neural blockade. In: Cousins MJ, Bridenbaugh PO (eds.) *Neural Blockade in Clinical Anesthesia and Management of Pain*, 3rd edn, pp. 1007–1061. Lippincott-Raven, Philadelphia, PA.
3. **Brown DL**, **Bulley CK**, **Quiel EC** (1995) Neurolytic celiac plexus block for pancreatic cancer pain. *Anesth Analg*, **66**, 869–74.
4. **de Leon-Casasola OA** (1999) Neurolytic blocks of the sympathetic axis for the treatment of visceral pain in cancer. *Curr Rev Pain*, **3**, 173–7.
5. **Eisenberg E**, **Carr DB**, **Chalmers TC** (1995) Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. *Anesth Analg*, **80**, 290–5.
6. **Yan BM**, **Myers RP** (2007) Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. *Am J Gastroenterol*, **102**, 430–8.
7. **Penman ID** (2009) Coeliac plexus neurolysis. *Best Pract Res Clin Gastroenterol*, **23**, 761–6.
8. **Erdine S** (2005) Celiac ganglion block. *Agri*, **17**, 14–22.
9. **de Oliveira R**, **dos Reis MP**, **Prado WA** (2004) The effects of early or late neurolytic sympathetic plexus block on the management of abdominal or pelvic cancer pain. *Pain*, **110**, 400–8.

10. **Wyse JM**, **Carone M**, **Paquin SC** *et al.* (2011) Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. *J Clin Oncol*, **29**, 3541–6.
11. **Rykowski JJ**, **Hilgier M** (2000) Efficacy of neurolytic celiac plexus block in varying locations of pancreatic cancer: influence on pain relief. *Anesthesiology*, **92**, 347–54.
12. **Yaksh TL**, **Rudy TA** (1976) Analgesia mediated by a direct spinal action of narcotics. *Science*, **192**, 1357–8.
13. **Faull RL**, **Villiger JW** (1987) Opiate receptors in the human spinal cord: a detailed anatomical study comparing the autoradiographic localization of [3H]diprenorphine binding sites with the laminar pattern of substance P, myelin and nissl staining, *Neuroscience*, **20**, 395–407.
14. **Yaksh TL** (1987) Opioid receptor systems and the endorphins: a review of their spinal organization. *J Neurosurg*, **67**, 157–76.
15. **Bernards CM** (2002) Understanding the physiology and pharmacology of epidural and intrathecal opioids. *Best Pract Res Clin Anaesthesiol*, **16**, 489–505.
16. **Palmer CM**, **Cork RC**, **Hays R** *et al.* (1998) The dose response relation of intrathecal fentanyl for labor analgesia. *Anesthesiology*, **88**, 355–61.
17. **Du Pen SL**, **Du Pen AR** (2003) The dilemma of opioid conversion in intrathecal therapy. *Semin Pain Med*, **1**, 260–4.
18. **Mitra S**, **Sinatra RS** (2004) Perioperative management of acute pain in the opioid-dependent patient. *Anesthesiology*, **101**, 212–27.
19. **Ruan X** (2007) Drug-related side effects of long-term intrathecal morphine therapy. *Pain Physician*, **10**, 357–66.
20. **Bedder MD**, **Burchiel K**, **Larson A** (1991) Cost analysis of two implantable narcotic delivery systems. *J Pain Symptom Manage*, **6**, 368–73.

Chapter 34

Useful apps and websites

Stephen B. Singh

Attitude

To enable each learner to:

- Consider that patients and families may rely on a variety of online resources and apps to obtain palliative care information.
- Realize that patients and families may wish guidance on how to evaluate these online resources and apps.

Skills

To enable each learner to:

- Demonstrate to patients and families how to evaluate health information online.
- Provide patients and families with useful websites for palliative care information in Canada.
- Evaluate the reliability of smartphone apps for palliative care information.

Knowledge

To enable each learner to:

- Point patients and families towards the best tools to evaluate online health information.
- Identify potentially useful apps for patients and families if asked.

Case 34.1

O.L. is a 72-year-old woman recently diagnosed with lung cancer metastatic to the brain. She presents with her daughter. At the first oncology appointment, various palliative therapies were discussed. They have searched online and printed out some information to discuss. They also have information about alternative therapies being discussed in an online social media forum. Which information can they trust?

Question 1. How can you help patients and families find reputable information online?

A new diagnosis of a life-limiting condition can be overwhelming. Increasingly, patients and families turn to the Internet to seek information. Much of the information found online is not reputable. Several tools exist to help patients determine the credibility of information online.[1,2] Dalhousie University Libraries have developed criteria to evaluate online health information:[2]

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- Credibility—assess the source, authors (including credentials, disclosures of bias, and sponsorship), and recency of information.
- Content—accuracy (testimonials are not evidence) and completeness (balanced information showing all sides), with appropriate disclaimers.
- Disclosure—site should identify who is collecting data, if anyone.
- Links—should be included, so users can identify other reliable sources.
- Design—should ideally be logically organized, with a search feature.
- Interactivity—should include feedback mechanisms.

Patients may use an online tool to evaluate health information.[1] Two more commonly used tools are:

- HONcode[3]—Health On the Net, a non-profit organization affiliated with the World Health Organization. It offers websites a certification seal after being assessed by their team.
- DISCERN[4]—funded by the British National Health Service (NHS), it provides a brief questionnaire to help users assess the quality of online health information.

Despite their ubiquity, patients and families should not rely on search rankings, which do not correlate with reliability, nor Wikipedia entries, which can be biased or inaccurate due to their reliance on crowd-sourced information.[5]

Question 2. What are some useful websites for palliative care information in Canada?

This list (see Table 34.1) is not exhaustive, but it provides a place to start. It was adapted from resources provided in Health Canada's Framework on Palliative Care in Canada.[6]
Local online resources may also be obtained through provincial or territorial medical associations.

Case 34.1 (continued)

O.L.'s daughter asks what apps you would recommend for her smartphone.

Question 3. How can you help patients and their families determine which apps are best?

Apps for smartphones are typically not approved by Health Canada and are often developed without a formal testing process by those without healthcare training.[7] The Canadian Medical Association has developed guiding principles to help physicians decide if to recommend an app.[8] These include:

- Endorsement by a professional or recognized association, medical society, or healthcare organization. It is important to remind patients that information provided by an app should not be construed as medical advice.[7]
- Usability. The Canadian Medical Protective Association (CMPA) also recommends that a physician personally uses an app before recommending it.[7]
- Reliability of information, including currency and lack of bias.
- Privacy and security.

Table 34.1 Useful websites for palliative care information in Canada

Website	Description
Canadian Virtual Hospice http://www.virtualhospice.ca/	Provides information and support to patients, families, healthcare professionals, researchers, and educators. Includes 'Ask a Professional' and a directory of services across Canada
Cancer Care Ontario: Palliative Care Toolkit for Indigenous Communities https://www.cancercareontario.ca/en/guidelines-advice/treatment-modality/palliative-care/toolkit-aboriginal-communities	Resources and references for First Nations, Métis, and Inuit
Caregiver Compass https://www.saintelizabeth.com/getmedia/89a61fed-0db8-487d-a8d7-d50b99cdb930/Caregiver-Compass-Online.pdf.aspx	Tools for caregivers to help manage their role, navigate healthcare systems, and coordinate financial and legal issues
Caregivers Alberta https://www.caregiversalberta.ca/	Caregiver support programmes, including e-learning
Government of Canada https://www.canada.ca/en/employment-social-development/campaigns/ei-improvements/adult-care.html	Information on federal employment insurance, caregiver benefits, and compassionate care benefits
Living My Culture http://livingmyculture.ca/culture/	Learn about various cultures, spiritualities, wisdoms, and traditions through stories
MyGrief and KidsGrief http://www.mygrief.ca/ and https://www.kidsgrief.ca/	Grief and bereavement resources for Canadians, from national and international grief experts
Pregnancy and Infant Loss Network https://pailnetwork.sunnybrook.ca/	Ontario-wide bereavement care for perinatal loss
Quality End-of-Life Care Coalition of Canada (QELCCC) http://www.qelccc.ca/projects-and-resources/educational-inventory-of-resources.aspx	Compilation of national end-of-life care organizations
Victoria Hospice https://www.victoriahospice.org/	Information on bereavement services and counselling, and local referrals

Source: data from Health Canada. (2018, December). Framework on Palliative Care in Canada. Available at https://www.canada.ca/content/dam/hc-sc/documents/services/health-care-system/reports-publications/palliative-care/framework-palliative-care-canada/framework-palliative-care-canada.pdf

- Avoiding conflict of interest.
- Does not contribute to fragmentation of health information.
- Demonstrates its impact on patient health outcomes.

Question 4. What are useful apps for palliative care information in Canada?

Most apps currently available in Canada for palliative care are targeted towards healthcare providers. However, some apps have useful information on national and provincial patient resources. As per CMPA (see above) physicians should test the apps first.[7]

Table 34.2 Useful apps for palliative care information in Canada

App	Description
Advance Care Planning (ACP) Speak Up Workbook https://www.advancecareplanning.ca/wp-content/uploads/2020/06/acpworkbook_form_en.pdf	A fillable PDF, rather than a full app. Encourages patients to fill out and provide their advance care plans to their substitute decision-makers
CancerControl Alberta My Care Conversations App https://www.albertahealthservices.ca/cancer/page16144.aspx	Allows patients and families to audio-record, with consent of both parties, important discussions with healthcare providers
Dynamed Plus App https://www.cma.ca/En/Pages/dynamed-plus-app.aspx	Available to Canadian Medical Association members. Evidence-based content online and offline
Pain Squad App https://itunes.apple.com/ca/app/pain-squad/id929781246?mt=8	Developed by Toronto's Hospital for Sick Children and available for iOS only. Children aged 8–18 can keep an electronic pain diary in a game-like environment
Pallium Canada Mobile App https://pallium.ca/equip-yourself/pallium-mobile-app/	Access to clinical tools, conversation tips, and national/provincial resources
RxTx https://www.pharmacists.ca/products-services/rxtxmobile/	Developed by Canadian Pharmacists Association. Includes drug and therapeutic options, Health Canada advisories, calculators, and more

This list of apps (see Table 34.2) is not exhaustive. Physicians are encouraged to contact their own medical associations for local resources. Some apps may be available for iOS, Android, Blackberry, or any combination thereof.

Conclusion

Patients and families will increasingly turn to online information and apps to help guide them through their palliative care journeys. The more that we, as physicians, can arm ourselves with these tools, the better we can serve our patients and families.

References

1. **Canadian Agency for Drugs and Technologies in Health** (2016) Evaluating the *c*redibility of *h*ealth *w*ebsites: *c*an *y*ou *t*rust Dr. Google? https://www.cadth.ca/sites/default/files/pdf/CADTH_credible_websites_onepager.pdf
2. **Dalhousie University Libraries** (2018) Evaluation of *h*ealth *i*nformation on the *w*eb. https://dal.ca.libguides.com/c.php?g=257155
3. **Health On the Net**. http://www.hon.ch/en/
4. **DISCERN**. http://www.discern.org.uk/
5. **Fahy E**, **Hardikar R**, **Fox A**, **Mackay S** (2014) Quality of patient health information on the Internet: reviewing a complex and evolving landscape. *Australas Med J*, **7**(1), 24–8.
6. **Health Canada** (2018) Framework on Palliative Care in Canada. https://www.canada.ca/content/dam/hc-sc/documents/services/health-care-system/reports-publications/palliative-care/framework-palliative-care-canada/framework-palliative-care-canada.pdf

7. **Canadian Medical Protective Association** (2016) Smartphone, smarter physician: safely recommending mobile health apps in your practice. https://www.cmpa-acpm.ca/en/advice-publications/browse-articles/2016/smartphone-smarter-physician-safely-recommending-mobile-health-apps-in-your-practice
8. **Canadian Medical Association** (2015) *Guiding principles for physicians recommending mobile health applications to patients*. https://www.cma.ca/sites/default/files/2018-11/cma_policy_guiding_principles_for_physicians_recommending_mobile_health_applications_to_patients_pd1-e.pdf

Chapter 35

Response to suffering

Deborah Dudgeon, Leonie M. Herx, and Susan MacDonald

Attitude

To enable each learner to:

- Appreciate that suffering is inherent to end of life.
- Recognize that suffering is a subjective experience and remain non-judgemental.
- Understand that suffering is intensely personal and a threat to an individual's personhood.
- Reflect on their own responses to suffering.

Skills

To enable each learner to:

- Utilize tools and interview techniques to explore and assess an individual's suffering.
- Develop a supportive approach to address the suffering of patients approaching end of life.
- Know how to approach a person who requests a desire to die.

Knowledge

To enable each learner to:

- Understand the role that supportive counselling plays in addressing suffering.
- Describe an approach for providing dignity-conserving care.
- Describe the different categories of interventions available to help address suffering.
- Realize the difference between an expression of a desire to die versus a request for a medically provided death.

Case 35.1

M.H., 59, has glioblastoma. She is too unsteady to walk and needs assistance with personal care. She is developing dysarthria and some vision problems, making communication somewhat challenging. She can no longer enjoy her hobbies (reading and knitting). She spends her days sitting in a recliner listening to the television. She is fully aware of her prognosis (she cared for an aunt with glioblastoma several years ago) and is adamant that she does not want to experience what she saw her aunt go through. She has decided that she wants to hasten her death and asks you to 'end it'. Her daughter is supportive of her choice, but her husband and son feel she should be transferred to hospital and managed there. The patient is experiencing severe

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distress over her husband and son's lack of understanding of her suffering and desire to die. The family is now divided and not speaking to each other. The patient sees you for symptom management and advice.

Question 1. What is suffering? What can contribute to a person's suffering?

Suffering is an intensely personal experience that is unique and particular to that person. Suffering is experienced by the whole person and can be caused by, or manifest itself in, the physical, psychological, social and/or spiritual/existential domains of an individual's life.[1] Cassell defines it 'as the state of severe distress associated with events that threaten the intactness of person'.[2] He states that 'suffering occurs when an impending destruction of the person is perceived [and] it continues until the threat of disintegration has passed or until the integrity of the person can be restored in some other manner', and 'that it can occur in relation to any aspect of the person'.[2] People are very complex and the threat to their personhood, Cassell suggests, can originate from their: past; culture and society; roles; associations and relationships; body; unconscious mind; political being; secret life; perceived future; and transcendent-being dimension.[2] Terms that are often used synonymously with 'suffering' include: demoralization; existential distress; psycho-existential suffering; psycho-spiritual distress; spiritual pain; and total pain.[3]

Suffering among those facing a life-limiting illness is a common phenomenon as terminal illness is an assault on the whole person. Over 90% of terminally ill patients in some studies report experiencing suffering.[4] In those studies that distinguished between physical and non-physical forms of suffering, about 50% of participants attributed their suffering to physical symptoms and the other half to psychological, existential, and social factors.[5,6] It is thought that there are non-physical forms of suffering that are intrinsic to the dying process and these include: death anxiety, loss, feeling burdensome, loneliness, and worry for family.[7]

Suffering is subjective and personal, such that two people with apparently identical challenges may have totally different perceptions of their suffering. In a study designed to examine the causes and correlates of suffering among patients with advanced cancer, Wilson and colleagues found that almost half (49.3%) of respondents did not consider themselves to be suffering and 24.9% felt that they suffered only mildly. Physical symptoms, psychological distress, and existential concerns were predictive of participants reporting suffering. Those who had moderate to extreme levels of suffering were most distressed by their general malaise, weakness, pain, and depression. More than half of participants with moderate to extreme suffering fulfilled the criteria for a depressive or anxiety disorder, compared to fewer than 15% of participants with lower levels of suffering.[5]

Pain and suffering are often linked, but a person may have pain and not be suffering and suffer without any physical pain. In a study of 92 hospice patients with less than 6 months to live, 71% reported physical pain, while 92.5% reported suffering.[8] Pain, or other unrelieved symptoms, can also be the source of severe suffering as the individual's reserves are depleted and their personhood assaulted. On the other hand, suffering that is unacknowledged can present as an intractable symptom such as pain that is not responsive to usual interventions.[3]

In the case of M.H., she is certainly facing a number of challenges that threaten her sense of self and personhood. She has significant functional impairments that have required her to transition from living an independent life to becoming dependent on others for ambulation and personal care. Her ability to see and communicate are threatened. Her life has become confined to sitting in a chair, watching TV. She has witnessed the possible course that her illness will take. Her family is

divided. All aspects of her life—physical, psychological, social, and probably existential/spiritual, have been assaulted by this illness.

Question 2. How do you assess the nature of a person's suffering?

It is easy to believe that we know the source of M.H.'s or another's suffering, but as stated earlier, suffering is subjective, deeply personal, and unique to that person.

The fact that an individual is suffering may not always be obvious. It is important to observe for emotional clues such as anger, irritability, anguish, shock, despair, sadness, vulnerability, insecurity, fear, grief, panic, frustration, yearning, doubt, boredom, or jealousy.[3] People may cry, withdraw socially, appear uncommunicative, miss appointments, or not comply with treatment recommendations. The individual's cultural background will also influence how suffering is expressed and therefore must be considered when doing an assessment.

Health professionals should use compassionate questioning, empathic comments and acknowledgements, and kindness when obtaining a history from people. Attention should be given to discover any uncontrolled pain or other symptoms that are overwhelming and a possible source of suffering. A thorough assessment looking for an underlying depression or anxiety should be performed and clues that the person is distressed about their social situation examined. Some opening questions to provide insight into how the person is affected by their illness are: 'What should I know about you as a person to help me take the best care of you that I can?'; 'What has been the hardest part of this experience for you?'; and 'Who else or what else will be affected by what is happening with your health?'. As Cassell says, 'the only way to learn whether suffering is present is to ask the sufferer.'[2] Questions such as 'In an overall, general sense, do you feel that you are suffering?'; 'What is the main thing that is causing you to suffer'; or 'If you tried to explain what your suffering is like, what would you say?' can be helpful to open a discussion.

There are a number of formal assessment tools that assess suffering or spirituality and meaning.[9] The Pictorial Representation of Illness Self Measure (PRISM) has shown great validity and reliability for suffering assessment in a variety of healthcare settings.[10] The Faith, Importance, Community, Address/Action in care (FICA) tool[11] and the HOPE questions[12] help structure questions for taking a spiritual history. The concepts the HOPE questions address are: H—sources of hope, strength, comfort, meaning, peace, love, and connection; O—the role of organized religion for the person; P—personal spirituality and practices; and E—effects on medical care and end-of-life decisions.

Case 35.1 (continued)

While taking her history, you learn that she was only diagnosed with the glioblastoma a few months ago. She has had surgery to remove the tumour and this was followed by radiation which was completed a few weeks ago. She has not seen a medical oncologist as 'there was nothing they could do for her aunt'. She was tapered off dexamethasone about 2 weeks ago which was when many of her physical problems started to get worse. During the interview, she at times appears angry, very frustrated with her inability to express herself freely, and irritable with her daughter when her daughter tries to help her. At one point during the interview, M.H.'s daughter needs to leave the room to put more money in the parking meter. As soon as her daughter leaves, M.H. starts to cry. She says she is scared that she will end up like her aunt who died alone after a prolonged period of dependency and complete loss of her dignity. M.H. says she has always been the strong one but now finds herself lashing out at her family. She wonders why God is punishing her in this way as she has been a good person and attended mass regularly. She demonstrates many findings of depression.

Question 3. What approaches are helpful to address suffering?

As healthcare professionals, one of the most important things when caring for someone is to see the person they are or were, rather than just the disease they have. Not being treated with dignity and respect can lead to feelings of being a burden to others and undermine a sense of value and worth for the person. It is important for healthcare professionals to: be fully present in their encounters with patients; develop a trusting relationship and willingness to listen; and demonstrate that the patient's concerns have been heard.

Chochinov's A, B, C, D of dignity-conserving care[13] is a mnemonic to 'remind practitioners about the importance of caring for, as well as caring about, their patients' so that the person's sense of value is enhanced and not diminished by the care they receive. 'A' is for attitude and highlights the need for the healthcare providers to examine their own attitudes, assumptions, and biases to be sure that their perceptions reflect the patient's reality and not their own perspectives. 'B' is for behaviour which must be informed by the core values of kindness and respect and reflect caring and attentiveness to the whole person. 'C' is for compassion which requires caregivers to get in touch with their own feelings about suffering and how those feelings shape their approach to care and desire to relieve the suffering. 'D' is for dialogue which should be routinely used to acquaint the healthcare provider with aspects of the patient's life to provide context that must be known to provide the best care possible.

After completing a careful assessment and determining the presence, nature, and sources of an individual's suffering, it is important to determine which member of the multidisciplinary team can best respond. If the suffering comes from physical distress, the nurse, physiotherapist, occupational therapist, dietitian, or physician may be best positioned to intervene. The social worker, psychologist, psychiatrist, or spiritual care worker may be primed to take the leadership role in addressing psychosocial or spiritual suffering or the patient may have these supports in the community already.

A diagnosis of advanced cancer can cause significant suffering as the person tries to continue living despite an imminent awareness of the fact that he or she is dying. A recent study[14] of people living with advanced cancer described five interconnected phases the patients experienced as they learned to live well despite the awareness of their dying. The first phase was 'struggling' with the diagnosis and sudden awareness of the possibility of dying. Over time, the participants realized struggling was counterproductive and *made a pivotal choice to let go of struggling and 'accept' the presence of advanced cancer and the problems it brought to their lives*. The second phase of acceptance was thought by participants to be essential to moving forward with living. The next phase 'living with advanced cancer' involved *working to minimize the effects of their illness problems on life* and living with strategies such as: *making life adjustments* (such as accepting assistance); *maintaining a positive attitude* (choosing to see the positive); and *focusing on the 'normal' aspects of their lives* and *hoping*. The next phase was 'sharing the illness experience' and involved *maintaining family and social relationships* so there were people to count on for support but also involved *protecting loved ones* to minimize their suffering. The final phase to move from living the disease to living life fully was termed 'Reconstructing Life'. The characteristics of this phase were that people *shifted attention to outside of themselves* and made contributions to family, community, and/or society and they *learned to live in the moment*. People described being 'intentionally present to attend to moments of joy or beauty' and controlling their thoughts by *actively stopping their thinking about their disease and dying*.

The findings of a qualitative study[1,15] involving interviews of patients with life-threatening illnesses suggested a number of strategies to improve quality of life and relieve existential

suffering: identifying sources of meaning, both positive and negative before and during the person's illness; exploring the creation of a life narrative and possible legacies for loved ones; exploring sources of existential anguish before and during illness; attending to dreams as clues to sources of existential distress; identifying sources of healing connections before and during illness; minimizing uncertainty; identifying and supporting expression of fears; identifying defence mechanisms that increase denial, distancing, and closure to others; promoting a sense of security through creation of a calm, pleasant atmosphere characterized by efficiency, accompaniment, and caring; and promoting strategies that bring the person into the present moment such as meditation, music, or discussion of their cherished interests.

Randomized controlled trials or controlled trials evaluating interventions to help reduce suffering can be categorized as: psycho-educational; meaning-centred; stress reduction; hope-centred; supportive–expressive; spiritual; and other. *Psycho-educational interventions* include education programmes, problem-solving, coping skills training, expression of emotion, and social support. *Meaning-centred interventions* include therapist-guided life reviews, individual psychotherapy focused on meaning, and meaning-centred group psychotherapy. *Stress reduction interventions* include yoga, mindfulness, meditation, and cognitive behavioural stress management. *Hope-centred interventions* encompass both individual and group interactions designed to instil, enhance, and maintain aspects of hope in the patients. *Supportive–expressive approaches* encompass both supportive group and individual therapies such as telephone therapy, forgiveness therapy, and face-to-face, telephone, and Internet-based support groups. *Spiritual interventions* include multidisciplinary educational sessions, support groups, body–mind–spirit therapy, spiritual counselling, and a brief semi-structured inquiry into religious/spiritual concerns. *Other* interventions include music therapy, art therapy, a creative art study with a mixture of movement to music, writing, and drawing, expressive writing, animal-assisted therapy, and hypnotherapy.[3]

Question 4. Can all suffering be relieved? How do you address persistent suffering?

Suffering is not an option in human life[16] and suffering at the end of life is intrinsic to the dying process.[7] Dying is hard and involves fear of death itself, multiple losses, feeling like a burden, loneliness, and worry for family. As health professionals, we are not always able to help people find meaning in their suffering or move beyond it. At these times, 'some of the best care that can be provided to those who suffer is to simply sit and try to bear what is unbearable' with the person.[7] This validation of suffering, rather than responding to it as if to fix or treat it, may result in some relief for patients and families.[17] It takes tremendous strength and courage to stay with suffering that is unchangeable. It challenges the clinician with their own limitations, vulnerability, and mortality. The impact of the multiple losses inherent in the dying process, the anxieties and fears about what happens after death, the feeling of being a burden, and the worry about family may not be able to be relieved, but they can be validated and normalized. This can help patients and families not feel alone.

Where the individual's suffering significantly impairs their ability to function and live their life, medications can be considered. Depression should be ruled out or treated, and anxiety appropriately treated with anxiolytics. In the last hours to days of life, proportionate palliative sedation can be considered to address unrelieved suffering that is due to refractory physical, psychological, and/or existential/spiritual symptoms, and delivered as per recommended guidelines (see Chapter 20).

Case 35.1 (continued)

You started M.H. back on dexamethasone 8 mg in the morning and at noon, and recommended she sees a medical oncologist as there have been significant advances in systemic therapies for glioblastoma since her aunt had been treated. You arranged for her to meet with a social worker and subsequently her family went with her as well. The steroids improved her vision, speech, and ambulation, as did the referral to physiotherapy. She was started on temozolomide and tolerated the treatment well. When you next saw her, she was much more positive and hopeful. The tensions with her son and husband had reduced as they had acknowledged their fears of losing her, not being able to care for her, and feeling helpless to assist her. She knew that her improvement would not continue forever, but she was hopeful for a few more months at least as there were things she still wanted to do. She was no longer interested in hastening her death.

Question 5. Can patients request a hastened death?

Patients can make informed decisions to forgo or withdraw life-prolonging or life-sustaining medical therapies when it is no longer in keeping with their goals of care. In these cases, patients' deaths may be seen as 'hastened', but death results from progression of the underlying condition. Many patients make this choice when they feel their quality of life no longer warrants ongoing life-prolonging treatments and they want to focus on comfort and allow natural death.

In several countries and in some states in the United States, patients can also consider a legal option of ending their lives through euthanasia and assisted suicide. In euthanasia, a lethal dose of drug is provided, typically through injection by a healthcare practitioner, and in assisted suicide, a lethal dose of oral drug is prescribed by a healthcare practitioner that the patient will ingest on their own. In Canada, the legal term for euthanasia and assisted suicide is medical assistance in dying.

Question 6. Which patients can request euthanasia and assisted suicide?

In every country or state where euthanasia or assisted suicide (E/AS) are legally available, there will be criteria that outline who is eligible and regulations for the process that must be followed. Clinicians are urged to be aware of the legislation and professional practice requirements in their location of practice.

Question 7. Are euthanasia and assisted suicide part of palliative care?

The World Health Organization's (WHO) definition of palliative care does not support hastening death as part of palliative care[18] and the International Association for Hospice and Palliative Care's position is consistent with this guidance, stating that E/AS are in direct conflict with the WHO definition and that E/AS should not be part of palliative care practice.[19] The Canadian Society of Palliative Care Physicians' position that euthanasia and assisted suicide are distinct from palliative care is also consistent with this and advocates that palliative care should be offered and available for all patients, regardless of their end-of-life choices, including those choosing E/AS.[20]

Question 8. How should we approach a patient who requests a hastened death?

Many requests for E/AS are indications of suffering that can be ameliorated by palliative care supports and may be normal expressions of grief and loss faced at end of life, as described earlier in this chapter, rather than a specific request for wanting their life terminated. A request for hastened death should be fully and sensitively explored to understand the nature of a person's suffering and what supports can be offered to address/alleviate this or to accompany the person in their suffering. In countries where E/AS are legally available, a minority of patients may continue to express a desire for death and request termination of life through E/AS, despite having awareness of, or access to, care. Clinicians must be aware of the legal and professional requirements in their specific practice locations regarding E/AS.

References

1. **Mount BM**, **Boston PH**, **Cohen SR** (2007) Healing connections: on moving from suffering to a sense of well-being. *J Pain Symptom Manage*, **33**(4), 372–88. doi:10.1016/j.jpainsymman.2006.09.014
2. **Cassell EJ** (1991) *The Nature of Suffering and the Goals of Medicine*. Oxford University Press, New York, NY.
3. **Cancer Australia** (2014) *Clinical guidance for responding to suffering in adults with cancer*. Cancer Australia.
4. **Krikorian A**, **Limonero JT**, **Romain JP**, **Vargas JJ**, **Palacio C** (2014) Predictors of suffering in advanced cancer. *Am J Hosp Palliat Med*, **31**(5), 534–42. doi:10.1177/1049909113494092
5. **Wilson KG**, **Chochinov HM**, **McPherson CJ** *et al.* (2007) Suffering with advanced cancer. *J Clin Oncol*, **25**(13), 1691–7.
6. **Rujs C**, **Kerkhof A**, **van der Wal G**, **Onwuteaka-Philipsen B** (2013) The broad spectrum of unbearable suffering in end-of-life cancer studied in Dutch primary care. *BMC Palliat Care*, **11**(12), 1–10. doi:10:10.1186/1472-684x-11-12
7. **Rattner M**, **Berzoff J** (2016) Rethinking suffering: allowing for suffering that is intrinsic at end of life. *J Soc Work End-of-Life Palliat Care*, **12**(3), 240–58.
8. **Baines BK**, **Norlander L** (2000) The relationship of pain and suffering in a hospice population. *Am J Hosp Palliat Med*, **17**(5), 319–26. doi:10.1177/104990910001700509
9. **Krikorian A**, **Limonero JT** (2013) Suffering assessment: a review of available instruments for use in palliative care. *J Palliat Med*, **16**(2), 130–42. doi:10.1089/jpm2012.0370.
10. **Buchi S**, **Sensky T**, **Sharpe L**, **Timberlake N** (1998) Graphic representation of illness: a novel method of measuring patients' perceptions of the impact of illness. *Psychother Psychosom*, **67**(4–5), 222–5.
11. **Borneman T. Ferrell BI**, **Puchalski CM** (2010) Evaluation of the FICA tool for spiritual assessment. *J Pain Symptom Manage*, **40**(2), 163–73. https://doi.org/10.1016/j.jpainsymman.2009.12.019
12. **Anandarajah G**, **Gowri A**, **Ellen H** (2001) Spirituality and medical practice: using the HOPE questions as a practical tool for spiritual assessment. *Am Fam Physician*, **63**(1), 81–9.
13. **Chochinov HM** (2007) Dignity and the essence of medicine: the A, B, C and D of dignity conserving care. *BMJ*, **335**(7612), 184–7.
14. **Arantzamendi M**, **Garcia-Rueda N**, **Carvajal A**, **Robinson CA** (2018) People with advanced cancer: the process of living well with awareness of dying. *Qual Health Res*, **30**, 1143–55. doi:10.1177/1049732318816298
15. **Boston P**, **Bruce A**, **Schreiber R** (2011) Existential suffering in the palliative care setting: an integrated literature review. *J Pain Symptom Manage*, **41**(3), 604–18. doi:10.1016/j.jpainsymman.2010.05.010
16. **Kenny N** (2017) *Rediscovering the Art of Dying*. Novalis Publishing Inc, Toronto, ON.

17. **Currow D**, **Hegarty M** (2006) Suffering—at the bedside of the dying. *Journal of Religion, Spirituality and Aging*, **18**(2–3), 123–36. doi:10.130/j496v18n02_10
18. **World Health Organization** (2002) *National Cancer Control Programs: Policies and Management Guidelines*, 2nd edn. World Health Organization, Geneva.
19. **De Lima L**, **Woodruff R**, **Pettus K** *et al*. (2017) International Association for Hospice and Palliative Care Position Statement: euthanasia and physician-assisted suicide. *J Palliat Med*, **20**(1), 1–7.
20. **Canadian Society of Palliative Care Physicians** (2019) *Key messages: Palliative Care and Medical Assistance in Dying (MAID)*.

Chapter 36

Public health palliative care

Denise Marshall and Doris Barwich

Attitude

To enable each learner to:

- Appreciate that social needs, including isolation and lack of access to social supports, are key issues for patients with chronic and serious illness and lead to poor quality of life and poor health outcomes.
- Recognize the limits of health service provision of palliative care.
- Recognize that prevailing approaches to palliative care focus on biomedical aspects of care.
- Recognize that societal engagement and culture shift are necessary to truly meet the needs of our patients living with serious illness and approaching end of life.

Skills

To enable each learner to:

- Identify key social factors contributing to a patient's care and well-being.
- Recognize and foster community capacity and community engagement to ensure whole person care.
- Articulate the importance of public health approaches to palliative care.

Knowledge

To enable each learner to:

- Understand the application of the World Health Organization (WHO) charter for public health when applied to palliative care.
- Discuss strategies for incorporating a public health approach into palliative care, based on the five core tenets of the Ottawa Charter for Public Health.
- Understand the 95/5 principle when addressing patients' needs.
- Understand how to incorporate the principles of health promotion into palliative and end-of-life care.

Case 36.1

I.S. is a 67-year-old woman who was diagnosed a year ago with Stage 3 ovarian cancer. She has received surgical and oncological treatments, and recently discovered that her disease has progressed to Stage 4. She has had problems with constipation and occasional signs of early bowel obstruction. Although she has not been hospitalized, she has gone to the emergency department three times in the last 2 months. Her oncologist has

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transferred care to the family physician for 'symptom management' and to monitor her bowels. I.S. sees her family doctor every few weeks and home care nurses call her every 2 weeks. Most clinic appointments are spent going over her current status and her family physician feels she needs 'lots of reassurance'. She always attends alone and seems distressed at the start of every visit, but a bit more relaxed at the end, despite no real changes in her medical care plan.

I.S. has only lived in this community for 8 years after downsizing and taking early retirement to care for her 84-year-old husband with progressive dementia. She has been married for 27 years and does not have children of her own. Her husband has two grown children living in another province, whom she rarely sees. She cared for her husband for over 10 years prior to his admission 18 months ago to a long-term care facility and his care is all consuming for her. She has not had time for personal pursuits nor has she made many friends. She now finds visiting her husband exhausting and feels guilty for not going to see him daily.

Question 1. What are I.S.'s unmet needs?

I.S., like many Canadians, is facing her uncertain future alone and is quite socially isolated. Studies indicate that up to 75% of visits to a family doctor in the last year of life are not for medical issues, but rather for social issues—reassurance, affirmation, and accompaniment. Without strong social supports, I.S. seeks out support in the emergency department and from her family physician and home care nursing.[1] While she has moments of feeling 'better', often when she is with her clinicians, these moments are fleeting. Most of the time, she is on her own at home and identifies that her sense of well-being is quite low. She admits to being lonely and worried about what will happen to her and to her husband when she is gone.

Question 2. Would you consider this to be a 'public health' issue?

The WHO would say a situation is a *public health issue* when it meets the following five criteria:[2]

- Prevalence.
- Impact on society.
- Preventable aspects of this condition.
- Effective interventions available.
- Equity considerations.

I.S.'s concerns are common among people nearing end of life when the anxiety of attempting to deal with multiple losses and concerns without adequate supports can be overwhelming. Dying and death are universal conditions faced by 100% of citizens everywhere. In most western jurisdictions, 1% of the population is in the last year of life, thus profoundly meeting the *prevalence* criteria.[3] Considerable evidence demonstrates that a 'bad death' experience and unattended grief (and bereavement) have a measurable, detrimental impact on bereaved family members and clinicians.

Many aspects of I.S.'s 'condition' are also *preventable*. These include loneliness, unattended fears and worries, poor symptom control, avoidable emergency room (ER) visits, and even existential suffering. There is a growing body of evidence that *early identification* of whole person needs in a serious illness trajectory allows for integration of proactive care and the mobilization of social supports.[4] These *interventions*, when offered early ('upstream'), have the best outcomes for an optimal end-of-life journey. Evidence-based *interventions* exist for all domains of distress that may be experienced as part of the dying process (physical, psychosocial, emotional, and spiritual). The

dying are an inherently vulnerable segment of any society; self-advocacy may be challenging and access to care difficult. Therefore, issues of *equity* almost always exist.[5]

Question 3. How can a 'public health approach to palliative care' be undertaken?

The WHO's approach to public health, as defined in the Ottawa Charter (1986),[2] has been applied to palliative care in many jurisdictions around the world to inform societal approaches, systems of care, and better patient care. Its five key principles are:

- Building healthy public policy.
- Creating supportive environments.
- Strengthening community action.
- Developing personal skills.
- Reorienting health services.

Any jurisdiction, community, or programme can adopt an approach that intentionally attends to one or more of these principles.[6] Virtually every area of medicine has a public health agenda as a component of care. This helps develop a wider community context within which health services can make their most effective contribution. For palliative care, it means involving the 'well' and engaging and mobilizing supports within communities and society for what has been coined 'the other 95%'—that portion of the last year of a person's life that is NOT spent with a healthcare provider.[7]

Successful initiatives in Canada and internationally have focused on community engagement, mobilization, and death literacy through various public engagement strategies, including public events, art shows, death cafes, etc. Many jurisdictions have formed strategic partnerships with community-based organizations, including neighbourhood housing, seniors housing groups, hospice societies, faith groups, and businesses. The goal of these 'Compassionate Communities' initiatives is to effect a culture shift in our society and to normalize issues associated with chronic illness, death and dying, and loss and grief, and foster a society in which '*palliative care is everybody's business*'.[8]

The Compassionate Communities movement is an end-of-life application of the WHO Public Health Charter and also utilizes the WHO Healthy Cities model. Community and health sectors create participatory partnerships to attend to the social aspects of care to enable patient- and family-centred care within circles of support that lead to increased quality of life and well-being.[9]

Question 4. Is there evidence that such approaches could enhance I.S.'s well-being at this time?

I.S. may benefit from mobilization of a circle of care in her surrounding community. Neighbours can help with everyday tasks and community volunteers could take her to appointments or to visit her husband. Friendly visitors for her husband may alleviate her worry for him once she is no longer able to visit him herself. Peer support from other caregivers may also be welcome. Having a trusted person to speak with when she feels anxious or worries that her symptoms are escalating may help avoid ER visits. She may benefit from advance care planning education offered by many community organizations. Her lack of knowledge or low death literacy about the natural trajectory of Stage 4 ovarian cancer may be contributing to her worry and make care planning difficult for her. A trained hospice volunteer may be key to provide support around her fears of dying and

accompaniment. She may enjoy contact with her former work colleagues and contact with her past employer may uncover benefits from her workplace for end-of-life care.[10]

Health systems, government agencies, health service groups, and communities are beginning to incorporate public health palliative care into their work plans, funding initiatives, and programme goals. The evaluation and assessment of the impact of such community engagement, mobilization, and public health approaches to palliative care, although in their infancy, are gaining traction.[11] Large-scale studies have shown the impacts of societal engagement and social networks on well-being and resiliency on validated measures. Emerging evidence also suggests that public health approaches to palliative care have measurable impacts in health service utilization. Collaboration among traditional palliative care providers, public health researchers, and those pursuing community partnerships and public engagement is now articulating new impact and evaluation measures. National and international organizations such as Pallium Canada,[12] the Canadian Hospice Palliative Care Association, and the BC Centre for Palliative Care,[13] as well as global initiatives such as Public Health Palliative Care International,[14] are leading the way.

References

1. **Marshall D**, **Kortes-Miller K** (2018) Was the 5th International Public Health Palliative Care Conference 2017 Canada's tipping point?—a meeting report. *Ann Palliat Med*, **7**(Suppl 2), S130–4. doi: 10.21037/apm.2018.03.07
2. **World Health Organization** (1986) *The Ottawa Charter for Health Promotion*. https://www.who.int/healthpromotion/conferences/previous/ottawa/en/
3. **Environmental Scan for Strengthening Residential Hospice Care in Ontario** (2015) *Report of the Residential Hospice Working*. Ontario LHINs and Ontario Ministry of Health.
4. **Holt-Lunstad J**, **Smith TB**, **Layton JB** (2010) Social relationships and mortality risk: a meta-analytic review. *PLoS Med*, **7**(7), e1000316. https://journals.plos.org/plosmedicine/article/file?id=10.1371/journal.pmed.1000316&type=printable
5. **Stephen AI**, **Macduff C**, **Petrie DJ** *et al.* (2015) The economic cost of bereavement in Scotland. *Death Stud*, **39**(3), 151–7. doi: 10.1080/07481187.2014.920435
6. **Abel J**, **Walter T**, **Carey LB** *et al.* (2018) *BMJ Supportive & Palliative Care 2013*, **3**, 383–8. *BMJ*, **363**, k4299. https://doi.org/10.1136/bmj.k4299
7. **Rosenberg JP**, **Horsfall D**, **Leonard R**, **Noonan K** (2015) Informal caring networks for people at end of life: building social capital in Australian communities. *Health Sociol Rev*, **24**(1), 29–37. doi: 10.1080/14461242.2014.999400
8. **Kellehear A** (1999) Health-promoting palliative care: developing a social model for practice. *Mortality*, **4**(1), 75–82.
9. **Hassan E** (2015) *The public health approach to palliative care. Principles, models, and international perspectives*. https://bc-cpc.ca/publications/white-papers/palliative-care-is-a-public-health-issue/
10. **Kortes-Miller K** (2018) *Talking About Death Won't Kill You*. ECW Press, Toronto, ON.
11. **Sallnow L**, **Heather Richardson H**, **Murray SA**, **Kelleahear A** (2016) The impact of a new public health approach to end of life care: a systematic review. *Palliat Med*, **30**(3), 200–11.
12. **Pallium Canada.** https://pallium.ca/equip-yourself/toolkits/
13. **BC Centre for Palliative Care**. *Compassionate Communities Toolkit*. https://bc-cpc.ca/all-resources/community-organizations/compassionate-communities-toolkit/
14. **Public Health Palliative Care International.** *Creating Compassionate Communities.* https://www.phpci.info/

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