An Integrated Treatment Pathway for Treating Diabetic Foot Ulcers and Implications of Silver Resistance

Use of DACC Technology and Total Contact Casting

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Faculty Disclosures

Dr. Finley: Consultant – BSN Medical
Dr. McGuire: Grant/Research Support – BSN Medical, NuTech, Podometrics, TEI BioSciences; Consultant – BSN Medical, Devon Medical Products, Zeomedix; Scientific Advisor – Podiatric Footcare Association; Promotional Speakers’ Bureau – 3M, BSN Medical, Hollister, Medline, Smith & Nephew, Steadmed, TEI BioSciences; Stock Shareholder – Creative Footwear Technologies

• This continuing medical education activity includes device brand names for participant clarity purposes only, due to the presence of different branded versions of the same device. No product promotion or recommendation should be inferred.
Learning Objectives

• After completing this activity, participants should be able to
  – Explore the value of hydrophobic dressings in reducing bacterial colonization
  – Assess the prevalence and implications of silver resistance
  – Review the current literature supporting off-loading of diabetic foot ulcers to improve healing rates and the role of total contact casting as an evidence-based standard
  – Review case studies on the use of hydrophobic bacteria-binding dressings and total contact casting for the treatment of diabetic foot ulcers

Hydrophobic Bacteria-Binding Dressings and Total Contact Casting: Review of Current Literature and Case Studies

James McGuire, DPM, PT, CPed, FAPWHc

National Diabetes Statistics Report 2014

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>29.1 million diabetics in the United States – 9.3% of the population</td>
</tr>
<tr>
<td>Diagnosed</td>
<td>21 million people (all ages)</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>8.1 million people (all ages)</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>86 million people (20 years old and above)</td>
</tr>
<tr>
<td>New Cases</td>
<td>1.7 million new cases of diabetes were diagnosed in people 20 years and older in 2012</td>
</tr>
</tbody>
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Estimated Diabetes Costs in the United States, 2012

- **Total medical costs** (direct and indirect): $245 billion
  - **Direct costs**: $176 billion
    - Average medical expenditures for people with diagnosed diabetes were 2.3 times higher than for people without diabetes
  - **Indirect costs**: $69 billion


Diabetes

- 85% of all lower limb amputations in diabetics are preceded by a foot ulcer
- Diabetics who develop a foot ulcer have a 55x greater risk of infection
- If a DFU is open 30 days or longer it has a 4x greater risk of infection

DFU = diabetic foot ulcer.


Etiology of Neuropathic Diabetic Foot Ulcers

Vascular Disease  Neuropathy  Deformity  Lifestyle Compliance

Activity Compliance  Repetitive Stress  Footwear

Diabetic Foot Offloading: Goals of Treatment

- Low Plantar Pressure
- Prevent Re-injury
- Rapid Wound Closure
- Reduce Costs
- Stable Ambulation with Aides
- Assure Compliance


Transitional Approach to Offloading

- TCC/iTCC
- Wound isolation TCC
- Football dressing

- RCWs
- Carville healing sandal
- Felted foam

- OrthoWedge Shoe®
- Diabetic healing shoe

- Depth shoe with rocker sole

TCC = total contact casting; iTCC = instant total contact cast; RCWs = removable cast walkers.

What is a TCC?

“A snug fitting below the knee cast that protects insensitive limbs from repetitive trauma, promotes ulcer healing, and allows patients to ambulate”

— Dr. Paul Brand
Father of the TCC

TCC Systems Are Designed to Address Barriers to Utilizing the TCC as a “Gold Standard”

- Easy to use – no learning curve
- Shortened application time
- Not messy
- Lighter
- Cooler
- Increased patient acceptance
- Functionality of traditional TCC

Results of 9 TCC Studies

- Average healing time: 43.73 days
- Percent healed: 88.9%
  Helm 1984; Sinacore 1987; Walker 1987; Mueller 1989; Meyerson 1992; Birke 1992; Lavery 1997; Armstrong 2001; Birke 2002

Healing/Days to Heal
TCC vs iTCC vs RCW

Healing Rate

Healing vs Days to Heal

Indications for TCC

- Plantar ulceration Wagner grades I and II
  - UTHSC grade A0, 1, 2, or 3
- Neuropathic, pressure, traumatic
  - Avoid: arterial, venous
- Neuropathic fracture (Charcot)
- Post-reconstructive surgery

Don’t Let ‘em Take It Off!

- A higher proportion of patients with ulcers that were healed at 12 weeks in the iTCC group than in the RCW group (82.6% vs 51.9%; P=0.02).
- Of the patients with ulcers that healed, those treated with an iTCC healed significantly sooner (18.7 vs 15.2 days; P=0.02).

Contraindications for TCC

- Acute infection
- Fever
- Palpable lymph nodes
- Deep sinus tract or narrow deep wound
- Perfuse drainage
- Active dermatitis
- Excessive/fluctuating edema
- Claustrophobia
- Known noncompliance
- Arterial insufficiency
  - Ankle-Brachial Index <0.8
- Wagner Grades 3, 4, 5

TCC Complications

- A major area of concern is the risk of iatrogenic complications
- Complication rates range from 11%–30% of high-risk patients
- The vast majority of these complications are minor
- Wukich found that 93% of the complications are minor skin irritations and do not require a change in the treatment protocol
- The most important factor for decreasing the risk of iatrogenic complications is frequent cast changing
- The real fear is not producing a new ulceration but an infection that may develop at the site that would be attributed to the clinician!

What Is “Good” Diabetic Foot Wound Care?

- Debridement of nonviable tissue
- Maintain moist wound healing
- Bacterial management
- Reduce excess inflammation
- Exudate management
- Edema management
- Maximize limb perfusion
- Metabolic control and nutrition
- Biomechanical offloading

Advanced Dressings Designed to Address Bacterial Burden

- Silver (all dressing categories come with silver option!)
- Cadexomer iodine
- Pigmented foam
- PHMB
- Honey
- DACC

PHMB = polyhexamethylene biguanide; DACC = dialkyldiethylaminoethyl chloride.
The Spectrum of Wound Bioburden

Sterile → Contaminated → Colonized → Critically Colonized

Critical Point for Bioload Management?


Traditional Approach to Infection

• Systemic antibiotics
  - Systemic adverse effects, tissue damage, allergic reactions
  - Unable to reach tissues with reduced perfusion
  - Limited effect on biofilm colonies
  - Limited to specific "sensitive" bacteria
  - Produce antigenic, inflammatory cellular debris
  - Induce antibiotic resistance (methicillin-resistant S aureus, vancomycin-resistant enterococci)
  - Topical hypersensitivity reactions

European Wound Management Association.

Traditional Agents to Control Bioburden

• Debridement: surgical, mechanical, autolytic, enzymatic
• Wound cleansing: macro- or microlavage
• Topical antiseptics: silver, copper, PHMB, iodine, methylene blue, gentian violet, cadexomer iodine, hypochlorous acid, hydrogen peroxide, Dakin’s solution, povidone-iodine, honey
• Topical antibiotics: mupirocin, gentamycin, bacitracin
• NPWT
• Superabsorbent dressings: hydroconductive, hydroretentive

NPWT = negative pressure wound therapy.
Negative Aspects of Antiseptic Dressings

- High toxicity
  - Example: High levels of silver, povidone-iodine, and Dakin’s solution were demonstrated to have a negative effect on fibroblast and epithelial cell proliferation
- Allergy to the agent
- Risk of bacterial resistance, cytotoxicity, inflammation, or discoloration
- Killing of bacteria will result in the release of intracellular contents and endotoxins from destroyed cells into the wound


Combating Biofilms

- Physical removal of bacteria from the wound prevents aggregation of bacteria into microcolonies, thereby preventing them from producing the necessary "minimal threshold concentration" needed to begin biofilm formation
  - Debridement
  - Antibiofilm agents
  - DACC
  - Antiseptic/antibiotic cleansers or dressings
  - NPWT/superabsorbent dressings


Hydrophobicity of Microbes

- Wound pathogenic bacteria and fungi express cell surface hydrophobicity because of certain hydrophobic structures on their cell surfaces
  - For cell-to-cell communication (eg, DNA exchange)
  - To bind to molecules for nutrition
  - To bind to surfaces to rest
  - For protection against phagocytosis
  - To adhere to host tissue (eg, in the initial phase of wound infection)

DACC Hydrophobic Technology

Physical Binding of Bacteria and Fungi to DACC-Coated Fibers

- *S. aureus* (yellow), *P. aeruginosa* (purple), *Enterococcus faecalis* (blue), *Klebsiella* species (green), *Candida albicans* (orange)


DACC Technology

- Dialkylcarbamoyl chloride coating
- "Hydrophobic" molecular structure
- Irreversible binding of bacteria with hydrophobic molecules on its cell walls to the DACC-coated dressing material
- Once bound, the bacteria "inactivate" or exhibit a decreased rate of replication
  - Their metabolism slows down and they exhibit decreased production of bacterial toxins
- They can be removed from the wound in toto


Prophylactic Bacterial Binding

- Preventing the attachment of planktonic microorganisms to the wound surface interferes with the very first stage in biofilm formation
- Encouraging the attachment on an alternative surface reduces the opportunity for formation of microcolonies within the wound itself, preventing the development of the characteristic exopolysaccharide "slime" noted in biofilms

Many Virulent, Microorganisms Exhibit Hydrophobicity

- Some common microorganisms in infected wounds
  - Staphylococcus
  - Streptococcus
  - Klebsiella
  - Citrobacter
  - C albicans


Test: Replication of Bound Bacteria

- Dressing samples with bound bacteria
- Incubation for 24 hours
- Result: limited replication occurred


Rapid and Effective Bacteria Binding

- The in vitro test shows
  - DACC binds bacteria already within 30 seconds
  - After 2 hours, the DACC dressing continues to bind more bacteria

Reduction of Wound Odor and Exudate Levels

- In a clinical trial on nonhealing wounds by Sylvie Hampton, DACC dressings eradicated malodor and increased the number of nonodorous wounds
- Exudate levels were reduced considerably
- Highly exuding wounds moved to moderate exudation within 4 weeks of treatment

Promotion of Wound Healing

- In the Kammerlander trial on 116 colonized and infected wounds, the DACC dressing eliminated the infection signs in the majority of patients
- Nearly all wounds (93%) improved or healed completely in the documented period
- The wound status of previously nonhealing wounds progressed from black and yellow toward red and pink

The Importance of DACC Technology

- Avoids development of microbial resistance
- Avoids cytotoxicity and the release of inflammatory cellular debris
- No demonstrated allergies to DACC
- Avoids systemic contraindications
- Prevents accumulation of bacteria on the wound surface
- Reduces bacterial exo- and endotoxin release
- Safe, simple, cost-effective
DACC Dressing Indications

- DACC dressings are effective in all wounds where the primary goal is to remove microorganisms.
- Contaminated, colonized, or infected wounds, regardless of their etiology
  - Chronic wounds, such as diabetic foot ulcers, leg ulcers, and pressure ulcers
  - Postoperative dehisced wounds
  - Traumatic wounds
  - Wounds after excision or incision of fistula or abscesses
- DACC is also effective against dermal fungal infections.

Comparative Study of Two Antimicrobial Dressings in Infected Leg Ulcers: A Pilot Study

- 40 patients were randomly assigned to treatment with a silver hydrofiber dressing or a DACC dressing.
- Swab samples from ulcer beds were taken in order to quantify the bacterial load at inclusion.
- Analyzing bacterial load variation showed a significant reduction of bacterial burden on day 4 in both groups.
  - The silver hydrofiber group had an average bacterial load reduction of 41.6%.
  - The DACC group had an average reduction of 73.1% (p< 0.00001).


Case Studies
Questions?

Please do not hesitate to contact me if there is anything at all that I can do for you:

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215-255-5994

Background, Basics and Significance of Silver-Resistance

Phillip J. Finley, PhD
Background and Introduction

- Origin
- Explosion of silver utilization in medicine due to broad-spectrum antimicrobial properties
- Not just used in burn and wound care
- Surgical devices, implants, shunts, catheters, etc
- Concerns of widespread silver resistance have been raised
- Funding – publication

Introduction

Genetic Basis for Silver Resistance

We know that silver-resistant genes exist
- Plasmid pMG101, isolated from Salmonella
- Since then, sil-genes have been identified in Salmonella, Enterobacter, Escherichia coli, Pseudomonas, Acinetobacter, Klebsiella, and Staphylococcus aureus

Just because genes exist, does not mean they are expressed
- A few cases of bacteria able to grow in toxic levels of silver concentrations
- Pseudomonas stutzeri, originally cultured from a silver mine
- This level of phenotypic silver-resistant expression is unique and remains unseen in clinical bacteria isolated from patients
Initial Bacteria Screening

- Can we even find any?
- Increase probability

Cheap Screening Assay

250 µM


67 were capable of luxuriant growth on agar with 250 µM Ag⁺

Repeated for 859 isolates collected from patients

250 µM Ag⁺

Out of the 67 growers, how many had sil-resistant genes?

32 isolates yielded polymerase chain reaction products for sil + genes
20 being from Enterobacter and Klebsiella


**Minimum Inhibitory Concentration**

- Are any of the 32 isolates expressing the genes?

<table>
<thead>
<tr>
<th>Species</th>
<th>MIC (µM)</th>
</tr>
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<tbody>
<tr>
<td>Enterobacter</td>
<td>5500</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>5500</td>
</tr>
</tbody>
</table>

(*Ag*) in µM – representative MIC images.


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**Silver's Microbicidal Efficacy**

Can be accounted for by three primary mechanisms

1. Silver can bind directly to DNA, interfering with cell replication and transcription

2. Silver can bind to enzymes

3. Silver can bind to the bacterial cell wall, disrupting polysaccharide integrity and membrane fluidity

Quite unique capability

Clinical Significance

Antimicrobial efficacy against silver dressings?

- First looked at them qualitatively
- Corrected zone of inhibition testing
- Secondary cultures


Silver-Sensitive

*K pneumoniae*

CFU = colony-forming unit.


Silver-Resistant

*K pneumoniae*

Silver-Sensitive *E. cloacae*


### Clinical Significance

- Silver-resistant bacteria were at least 1000 X more resistant to commercially available silver-based wound dressings compared with their nonresistant counterparts

- **Current Clinical Studies**
  - Biofilm or silver resistance
  - Catheter surveillance

Clinical Comments/Criticism

- Only 2 out of 859 isolates (0.2%) were expressing the genes at time of analysis
- But 32 actually had the genes (3.7%)
  - Just because they weren’t expressed during testing doesn’t mean they can’t
- Remember, 67 were capable of growth during initial screening (~8.0%)
- We only looked at specific genes in 1 plasmid (there are potentially many different plasmids and genes)
  - For example: R478, pAPEC-O1-R, R27, and pUP1199


Clinical Comments/Criticism

Bacteria can’t share this plasmid above room temperature

Incompatibility Group HI Plasmids


Value of Hydrophobic Dressings

- Antimicrobial agent stewardship
- Nonsilver-based dressings
- Foundation of hydrophobic interactions
- Cell surface hydrophobicity


Value of Hydrophobic Dressings

- Sequestering and retention of microorganisms
- Passive mechanism for reduction of bioburden
- Addresses issues of resistance

Conclusions

• First clinical bacteria identified expressing clinically significant silver resistance
• The development of acute silver resistance would have significant consequences on wound care and patient outcomes
• Warning
  – Bacteria are resilient – they are going to figure out a way to survive
  – Silver antimicrobial stewardship

Q&A