Bacterial translocation (BT) is the passage of viable bacteria or their products from the intestines to extraintestinal sites. During the 1980s and 1990s, many experimental models were developed to prove that BT was a cause of sepsis, systemic inflammatory response syndrome (SIRS; see box on page 230), and multiple-organ dysfunction syndrome (MODS; see box on page 230). Recently, the paradigm shift has been that SIRS or MODS can cause BT. BT remains a very important phenomenon because it may initiate a proinflammatory response and be the nidus for an occult cause of sepsis.

PATHOGENESIS

A simple hypothesis was proposed to explain the occurrence of multiple-organ dysfunction in animals or humans without a known septic focus. It was believed that shock or trauma resulted in reduced perfusion and impaired oxygen delivery to the gut. The ensuing mucosal damage caused by ischemia/reperfusion (I/R) injury and oxygen stress resulted in gut barrier dysfunction, allowing translocation of bacteria and/or endotoxins into the systemic circulation. Mediators, from the gut or other reactive cells, were thought to induce a massive proinflammatory response, thus affecting distant organs.

Despite the considerable mass of evidence supporting the existence of BT in experimental animals, the clinical significance of BT was called into question when researchers were unable to culture bacteria from the portal or systemic blood in a series of human trauma victims. In addition, results were somewhat disappointing in a multicenter trial of critically ill humans in which selective gut decontamination was evaluated and antimicrobial agents were used aggressively to depopulate the gut of pathogenic gram-negative bacteria and fungi. No improvement in length of survival was noted despite a 50% reduction in the number of infectious complications in these patients.

The inability to culture bacteria from the portal vein of animals or humans with shock of recent onset led to some modifications in the original hypothesis of BT. It is now believed that the gut-derived factors contributing to distant organ injury are found in the mesenteric lymph nodes rather than in the portal blood and that actual bacteria are not necessary to initiate the systemic inflammatory response. The “two-hit” theory is one way of explaining the relationship between the gut and MODS (see box on page 230). The first hit is the initial damage, such as shock or trauma. The response is in accordance to the severity and amount of induced tissue damage. The first hit causes splanchnic hypoperfusion and primes the immune system by activating polymorphonuclear neutrophils (PMNs) and macrophages.
Hypoperfusion also causes a reduction in oxygen delivery to the tissues, therefore decreasing ATP production and other related cellular functions. Ischemia causes an increase in oxygen free radicals (OFRs) and causes gene transcription to produce cytokines and other inflammatory products.

The first hit, early SIRS, can be protective by producing more antiinflammatory than proinflammatory cytokines, but if the cascade continues, a second hit can exacerbate the injury. The second hit can be triggered by BT. Endotoxins are known to stimulate cytokine release, resulting in impairment of the immune system, coagulation system, and gastrointestinal (GI) mucosal barrier. The gut releases massive amounts of proinflammatory cytokines. These cytokines (i.e., tumor necrosis factor-α [TNF-α], interleukins [IL-1 and -6]) cause hemodynamic problems and tissue injury. Activation of PMNs, especially in reaction with OFRs, amplifies the inflammatory response. PMNs can add chlorine to react with hydrogen peroxide, thereby producing hypochlorous acid. When PMNs are activated, the conversion of oxygen to superoxide increases 20-fold. PMNs are attracted to the inflamed area via complement and cytokine stimulation. PMNs can add chlorine to react with hydrogen peroxide, thereby producing hypochlorous acid. When PMNs are activated, the conversion of oxygen to superoxide increases 20-fold. PMNs are attracted to the inflamed area via complement and cytokine stimulation. The PMN–endothelium interaction can lead to disseminated intravascular coagulation, microvascular thrombi, and organ dysfunction.

Excessive production of inducible nitric oxide synthase is stimulated by cytokines. Nitric oxide combines with OFRs to produce peroxynitrite, which causes vasodilation, depresses myocardial contractility, and adds to mucosal injury. This mediator can also cause cellular damage through lipid peroxidation, ATP and glutathione depletion, and mitochondrial dysfunction.

Transcriptional failure also occurs in patients with MODS. The genes produce more proinflammatory cytokines than antiinflammatory mediators, and the acute phase proteins are also decreased.

Further evidence that BT involves mesenteric lymph nodes rather than portal blood has been provided by a number of studies. Because the lungs are the first organ exposed to mesenteric lymph, acute lung injury after hemorrhagic shock or thermal injury in rats can be prevented or ameliorated by diverting mesenteric lymph flow. It has also been shown that mesenteric lymph (but not portal blood) collected after a shock episode activates PMNs, increases endothelial cell permeability, and even causes cell death in vitro. Mesenteric lymph nodes drain into the thoracic duct, which bypasses the reticuloendothelial system and goes directly to the lungs. High levels of endotoxins have been found in lymphatic fluid after shock, whereas blood cultures are often negative.

Another factor that has recently been shown to be important in the pathogenesis of BT is bacterial viru-
Bacterial translocation remains a very important phenomenon because it may initiate a proinflammatory response and be the nidus for an occult cause of sepsis.

pH through macrophage gene transduction. The bacteria can then be transported to more distant sites within the host.

Bacterial overgrowth also contributes to BT. Studies have shown that use of antacids in critical patients may lead to proximal gut colonization by virulent bacteria because of increased gastric pH. Colonization of the proximal gut has been associated with an increase in BT and septic morbidity.

GI BARRIER

The host’s defense system can be divided into four categories:

- Gut-associated lymphoid tissue (GALT)
- Gut–liver axis
- Mechanical properties
- Resident bacteria

GALT is the largest lymphoid system in the body. It comprises approximately one-half to two-thirds of lymphocytes in the body. The lymphocytes are located in Peyer’s patches, lymphoid tissue, between epithelial barrier. Conditions of poor perfusion, such as splanchnic ischemia associated with shock, also result in decreased epithelial cell turnover, cell death, and enhanced potential mucosal breakdown. Stress gastritis and ulceration are therefore common in critical patients.

A final factor that helps to maintain the normal GI mucosal barrier is the protective role of the normal indigenous microflora. Anaerobes are the most numerous bacteria in the GI tract. They compete with potential pathogens for nutrients and mucosal attachment sites, thereby inhibiting bacterial overgrowth with gram-negative bacteria. Antibiotic therapy often upsets the delicate balance of the GI microflora by selecting for gram-negative and resistant organisms while suppressing the more sensitive indigenous anaerobes. Other interventions that may disrupt the normal flora in critical patients include the use of H₂ blockers, which can result in bacterial overgrowth and colonization of the stomach, and the use of hyperosmolar enteral diets.

NUTRITION

Nutritional support of critically ill patients is important to decrease the catabolic effects of the disease.
“Bowel rest” for more than 3 days can cause deterioration in the enterocyte population, leading to mucosal atrophy, altered permeability, and decreased GI immunity. Early enteral feeding can improve splanchnic blood flow and modulate the immune response. Nutritional factors do improve gut barrier functions, although enteral feeding can be associated with complications such as diarrhea, cramping, bloating, vomiting, and ileus. Parenteral feeding is not without complication either, as it can cause thromboembolism, thrombophlebitis, hyperglycemia, hypertriglyceridemia, infection, and increased cost. A combination of parenteral and enteral nutrition may be advantageous because the luminal nutrients can aid enterocyte health while parenteral nutrition can decrease the amount of contents being fed enterally.

The type of diet fed may also be important. In mice, feeding a liquid diet resulted in BT, whereas feeding a solid diet of rat chow did not result in BT. Another nutrient that has received considerable study is glutamine. Glutamine is the preferred metabolic fuel for cells lining the small intestine and has been considered a “conditionally essential” nutrient in critically ill patients. It is essential for lymphocyte mitogenesis and enhances gut barrier function. Many studies in rodents have shown beneficial effects (i.e., reduced BT, thicker GI mucosa, increased survivability, enterocyte regeneration) by adding glutamine to enteral solutions. In cats, however, a glutamine-enriched diet was unable to prevent BT or attenuate permeability defects secondary to methotrexate-induced enterocolitis.

The preferred fuel of colonocytes is short-chain fatty acids. These are produced through fermentation of nondigestible carbohydrates, commonly referred to as fermentable fibers (i.e., pectin, β-glycan, lactulose). Insoluble fibers, such as cellulose, have trophic effects on the GI mucosa by promoting mucus production, stimulating epithelial cell growth, and preserving growth of normal microflora. Insoluble fiber is thought to stimulate release of trophic gut hormones, which can enhance gut barrier function. Current recommendations regarding optimal fiber type and dose are lacking, but research is ongoing. Preliminary animal studies have shown decreased BT, prevention of mucosal atrophy, and avoidance of cecal bacterial overgrowth after the addition of bulk fiber additives to enteral diets. Other dietary additives that may reduce BT include omega-3 fatty acids (fish oil products), arginine, nucleic acids, and antioxidants.

**TREATMENT**

BT can be a major player in the two-hit phenomenon and can cause exacerbation of the inflammatory cascade. It is important to prevent BT from causing secondary problems. The mucosal barrier is the first line of defense, and early resuscitation can curb the I/R injury, which can lead to BT.

IV fluid therapy with crystalloid and/or colloid fluids should be administered to maintain adequate blood pressure and GI perfusion (Table 1). A mean arterial
and may even facilitate offloading of oxygen in tissue. They are also nitric oxide scavengers, a property that may improve blood pressure in animals with hypotension secondary to hemorrhagic shock. Supplemental oxygen should definitely be administered if the pulse oximetry reading drops below 90% to 95%, but there is also evidence to support hyperoxygenation of patients in shock even when oxygen saturation is normal. In one study of experimentally induced hemorrhagic shock in rats, administration of 100% oxygen prevented BT and TNF-α gene expression compared with that in rats breathing room air. If available, gastric tonometry is an effective method of monitoring intramucosal pH and determining whether GI perfusion is adequate.

Positive inotropes, such as dobutamine or dopamine, may be necessary to maintain blood pressure and restore perfusion in septic patients. β-agonists also have anti-inflammatory effects that may reduce I/R injury. By increasing cyclic AMP, they are thought to stabilize leukocytes and reduce oxidant release.

Recent studies conducted in rodents with hemorrhagic shock have shown a beneficial effect of hypertonic saline (HTS). Rats treated with HTS showed attenuation of lung injury and reduced BT compared with rats resuscitated with lactated Ringer’s solution. HTS was shown to attenuate platelet-activating factor and postinjury priming of PMNs, thereby reducing the cytotoxic response. Timing may be important because early use may suppress neutrophil activation, thereby preventing or reducing lung damage. The effects of HTS are relatively short-lived but can be prolonged by adding a colloid, such as hetastarch, which has also been shown to decrease inflammation by attenuating PMNs.

Broad-spectrum antibiotics should be used in any animal exhibiting signs of sepsis or infection. Early diagnosis and surgical correction of areas of devitalized tissue or abscess drainage are paramount to successful case management.

The use of selective digestive decontamination is still very controversial. In most cases, mortality has not changed with combined use of topical and systemic antibiotics. BT was decreased in cirrhotic patients given selective decontamination in animal models, but in animal models, BT was decreased with the use of gentamicin. Steroids have been used in late phases of septic shock and have improved survival in gram-negative, but not gram-positive, sepsis. Testing for hypocortisolism in septic patients may be necessary to evaluate the animal’s need for cortisone. A study by Chaing et al suggested that a combination of steroids and colloids might be more beneficial as a reperfusion solution. Administration of steroids to compete against the proinflammatory response may be beneficial, but if the antiinflammatory forces are dominant, the use of steroids could be detrimental. Timing may be the answer to the steroid dilemma.

Reperfusion injury may be prevented with allopurinol or superoxide dismutase. Vitamins A, C, and E; selenium; β-carotene; and the amino acids cystine, glycine, and glutamine are all involved in the body’s antioxidant defense network. Dietary supplementation with antioxidants may be beneficial. Deferoxamine is an iron chelator shown to reduce oxidant damage in experimental studies, but its use has been limited because of side effects related to hypotension. Recent efforts to

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Crystalloids</td>
<td>90 ml/kg/hr IV (22.5 ml/kg/15 min and reevaluate)</td>
</tr>
<tr>
<td>Colloids</td>
<td>20 ml/kg IV</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Approximately 100–200 ml/kg/hr (nasal oxygen) without exceeding an FIO₂ of 60% for &gt;12 hr</td>
</tr>
<tr>
<td>Whole blood</td>
<td>20 ml/kg</td>
</tr>
<tr>
<td>Packed erythrocytes</td>
<td>10 ml/kg</td>
</tr>
<tr>
<td>Oxygen-carrying hemoglobin solutions</td>
<td>5–30 ml/kg</td>
</tr>
<tr>
<td>Dobutamine (dogs)</td>
<td>1–10 µg/kg/min CRI</td>
</tr>
<tr>
<td>Dopamine</td>
<td>3–8 µg/kg/min CRI</td>
</tr>
<tr>
<td>Hypertonic saline (7% sodium chloride)</td>
<td>4 ml/kg IV</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>1 g/25 kg PO q6–8h</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>1–2 mg/kg/day CRI</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>10 mg/kg PO q8h</td>
</tr>
</tbody>
</table>

Shock doses are a starting point, and endpoints for stabilizing vital signs must be met to determine whether to increase or decrease fluids.

CRI = constant-rate infusion.

FIO₂ = fraction of inspired oxygen.
combine deferoxamine with hetastarch have shown improved hemodynamics and reduced oxidant damage while avoiding toxic side effects. Pentoxifylline and lisofylline have been shown to attenuate lung injury and reduce BT in rats with hemorrhagic shock. These agents decrease tissue injury by inhibiting neutrophil adherence and decreasing cytokine release.

H₂-blockers have been blamed for an increase in bacterial overgrowth in the stomach that could create a possible source of aspiration pneumonia. Sucralfate may have the advantage of healing gastric ulcers and concomitantly decreasing BT without increasing gastric pH. It also protects mucus production, which decreases the occurrence of reperfusion injuries. Prokinetic drugs, such as metoclopramide and cisapride, are helpful in decreasing bacterial overgrowth by improving GI motility.

Glutamine is a source of energy and an important amino acid that carries nitrogen. It is also an important fuel for gut maintenance and repair. Because glutamine is unstable in total parenteral nutrition solution, it is not used as an additive. Experimentally, it has been shown to be helpful in enteral solution but no more helpful than intact proteins and peptides.

SUMMARY

The occurrence of BT has been well documented in experimental animal models of hemorrhagic shock, trauma, severe burns, cirrhosis, pancreatitis, and bacterial overgrowth. Translocation of viable bacteria and endotoxins into mesenteric lymph nodes and other gut-associated lymphatic tissue is thought to activate a complex interplay of mediators that initiates SIRS. Multiple humoral and cellular systems cause synthesis, expression, and release of inflammatory mediators, such as toxic oxygen radicals, proteolytic enzymes, adherence molecules, and various cytokines. A massive sustained proinflammatory response can ultimately result in irreversible multiple-organ dysfunction.

Because BT is associated with I/R, it is important to rapidly resuscitate patients to restore tissue perfusion. Nutrition, along with prokinetic drugs, protectants, and antioxidants, has shown benefit in preventing BT and its life-threatening effects.

REFERENCES


**ARTICLE #5 CE TEST**

*This article qualifies for 1.5 contact hours of continuing education credit from the Auburn University College of Veterinary Medicine. Subscribers who wish to apply this credit to fulfill state relicensure requirements should consult their respective state authorities regarding the applicability of this program. To participate, fill out the test form inserted at the end of this issue.*

1. **BT**
   a. is the passage of viable bacteria to extraintestinal sites.
   b. is the passage of bacterial products to extraintestinal sites.
   c. was thought to be a cause of MODS.
   d. all of the above

2. **Bacteria have been shown to be important in virulence because**
   a. all bacteria are considered virulent, especially gram-negative microbes.
   b. they can sense the vulnerability of the host when ileus occurs.
   c. they can sense the vulnerability of the host by detecting changes in temperature and pH.
   d. they are killed when they are phagocytized by macrophages.

3. **Which of the following statements regarding host immunity is false?**
   a. The host defenses against BT are composed of GALT, liver–gut axis, resident bacteria, and mechanical properties.
b. IgA is produced by B-cells and can be found in the mucous layer of the gut.
c. Ileus is not associated with BT because bacteria stay in the lower gut.
d. Anaerobes are the most numerous microbes in the gut and can help prevent potential pathogens from colonizing.

4. Therapy to prevent BT includes the use of
   a. steroids.
   b. hypotensive resuscitation.
   c. antibiotics, especially those against anaerobes.
   d. early enteral feeding.

5. Which of the following statements regarding nutrition is(are) true?
   a. Enteral feeding can cause diarrhea, cramping, and bloating.
   b. Parenteral feeding can cause hyperglycemia and thromboembolism and can cost more compared with enteral feeding.

6. Which of the following statements regarding glutamine is incorrect?
   a. It is metabolic fuel for enterocytes and is considered conditionally essential.
   b. It is essential for lymphocyte mitogenesis.
   c. When incorporated in feline diets, it has decreased BT in methotrexate colitis.
   d. It has been added to enteral diets to promote enterocyte regeneration.

7. Which of the following does not pertain to the "two-hit" theory?
   a. BT can be a major player in the second hit.
   b. The first hit can be associated with trauma.
   c. The amount of damage from the first hit is not proportional to the response of the host.
   d. The first hit caused by shock can cause splanchnic hypoperfusion and prime the immune system.

8. Which statement regarding early therapy is false?
   a. It is important to maintain adequate blood pressure and GI perfusion.
   b. If deprived of oxygen for more than 5 to 10 minutes, most cells can become temporarily or permanently damaged.
   c. Supplying oxygen at 1 L/20 lb via nasal tubes supplies an FiO₂ of approximately 20%.
   d. Fresh blood can carry oxygen and act as an antioxidant.

9. Which statement regarding therapy with blood or hemoglobin substitutes is false?
   a. Hemoglobin substitutes may enhance off-loading oxygen to tissue.
   b. Hemoglobin substitutes are nitric oxide scavengers, which may improve blood pressure.
   c. Fresh-whole blood given within 8 hours after collection will carry oxygen but will not supply coagulation factors.
   d. none of the above

10. Which of the following regarding prevention of BT is correct?
    a. Rapid resuscitation can help prevent BT.
    b. HTS should not be used as a resuscitation fluid.
    c. High doses of steroids can be beneficial in late septic patients.
    d. α-Agonists are vasopressive agents and have anti-inflammatory properties.