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Microecology of Infections Associated with Surgery and Trauma

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Trauma is one of the leading worldwide causes of death at present and fatal trauma cases are the fourth highest cause of death in youths. As a consequence of improved emergency medical treatment, early death rates (48 h post injury) have been significantly reduced. However, death rates resulting from trauma-related complications have not diminished. The most common and dangerous complication that can develop post surgery/trauma is infection caused by opportunistic pathogens, which pose a significant challenge to the healing process [1]. In addition to interference with the healing process and direct damage to infected tissues caused by the infecting organism, systemic complications, including acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), systemic inflammatory response syndrome (SIRS) and acute renal failure (ARF) can develop. These complications significantly exacerbate a patient's already deteriorating health and increase recovery times that correlate directly with increased mortality. Therefore, these infections are a major threat to trauma patients, early detection and control of respective infectious agents is essential in decreasing the rates of post trauma-associated morbidity and mortality.

19.1   Main Pathogenic Bacteria Associated with Surgical and Trauma-Related Infections

Damage to the epidermis or to physical barriers that maintain homeostasis between the body and the external environment provides an opportunity for opportunistic organisms to invade and establish infections. This process is facilitated by decreased immunity associated with various states of trauma and/or potential damage to internal tissues. Damage to internal physical barriers, including damage to the intestine can result in dysbacteria-related infections. Although strains and their respective distributions vary between countries, regions and even medical units, these types of infection have a similar presentation and can be treated in similar fashion. For example, it has been reported that the prevention and treatment of surgical and trauma-associated infections are similar between USA and UK, suggesting that differences in the causative agents of infections between these countries do not affect treatment modalities.

19.1.1   *Changes to the Spectrum of the Pathogenic Bacteria*

Due to the continuous improvement of anti-infection therapies (*e.g.* surgical procedures, post surgical support and critical care strategies) in recent years, a reduction in post-surgical and post-trauma-related infections has been observed. However, concomitant with the reduced rates of infection associated with these improvements has been the rise of increasingly drug-resistant bacteria that are also more virulent. The changes in the microbial landscape have required modifications in some cases to existing treatment protocols. Historically, Gram-positive bacteria were the primary pathogens associated with traumatic infections. However, the effective use of penicillin and related antibiotics during the developing years of the antibiotic era increased the number of infections caused by Gram-negative bacteria. Presently, due to the abuse and overuse of antibiotics, both Gram-positive and Gram-negative bacteria (in addition to fungal infections) have become associated with serious post trauma/surgical infections. There has also been a parallel increase in the number of nosocomial infections that pose an increasing threat to the success of clinical therapies and the prevention of post-traumatic and post-surgical infections.

19.1.1.1   The Rise of Drug-Resistant Bacteria and Changes in Pathogenicity

Antibiotics were developed to control bacterial infections and penicillin, the first antibiotic discovered and the first prepared for commercial use, had a significant effect on the control of both Gram-positive and Gram-negative cocci and its use spread worldwide. However, excessive and undisciplined use of antibiotics, combined with patients not completing their respective treatment doses has

resulted in the selection of bacterial strains resistant to multiple classes of antibiotics (sometimes accompanied with increased virulence). To date, bacterial infections represent a serious hazard to human health, and these types of infections are becoming more common and refractory in nature. The clinical spectrum of infections currently is focused on infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin resistant *Streptococcus pneumoniae* (PRSP), Vancomycin-resistant Enterococcus (VRE), Super-spectrum-Lactamase (SSBL) bacteria, axiomatic multi-platform C bacteria (AmpC), metallo-β-lactamase bacteria, *M. tuberculosis*, coagulase-negative staphylococci, *Escherichia coli*, pneumonia crayresearch bacteria, *Pseudomonas aeruginosa*, *Acinetobacter baumanii* and *Enterobacter cloacae*. Because of the development of resistant strains and changes in the pathogenic spectrum, post-operative and post-traumatic infections have become more and more difficult to control.

19.1.1.2   Changes in the Pathogenic Spectrum of Community Acquired Infections

Community acquired infections often occur at the injury site and, despite the use of preventative measures (including antibiotics), the significant incidence and severity of post-traumatic infections needs to be addressed. Improvements to support therapies facilitating the survival of severe trauma patients are threatened by emerging antibiotic-resistant pathogens, making treatment of post-traumatic infections challenging, especially since even the best treatment options are not guaranteed to prevent infections.

Wound infections. Most primary wound suture infections are caused by *S. aureus*. Farming accidents and other outdoor traumas often include inoculation of wounds with Gram-negative bacteria, including *P. aeruginosa*. The identification of the causative agent of industrial accident or mechanized farming trauma-related wounds is very important since atypical bacteria may be present on the equipment associated with these accidents. Suppurative infections caused by insect stings are primarily caused by *S. aureus*, therefore, if a Gram-positive cocci is identified, the likely cause of the infection can be deduced without additional microbiological testing.

Bacterial infections. Bacterial infections can develop into necrotizing fasciitis that can be caused by group A *Streptococcus*, aerobic or anaerobic bacteria. Necroinflammation may develop relatively slowly in infections caused by multiple organisms. Various gram-negative enteropathogens that are typically obligate anaerobes are associated with infections resulting from intestinal puncture wounds, and *S. aureus* infections can also result from these types of trauma. Group A Streptococcus and *S. aureus* are also associated with toxic shock syndrome resulting from hemodynamic instability and soft tissue necrosis. In addition, deep wound infections can be caused by gangrenous anaerobic spore-forming bacteria, and drainage of respective wounds is typically associated with short gram-positive bacteria.

Open fractures. Soft tissue infections (STI) are frequently associated with open

fractures, and infections are typically caused by *S. aureus* infections. However, nosocomial infections occur more frequently than infections caused by environmental wound infections.

Intra-abdominal infections. Bacteria associated with peritonitis resulting from intestinal trauma are typically of intestinal origin. However, celiac cultures may not be an effective means of identifying microbial species during emergency laparotomies, and the nature of the respective pathogens is consistent with the region of the intestine damaged. Therefore, the accuracy of hypothesizing, as to the nature of the causative agent responsible for respective infections resulting from bacteria of intestinal origin, is limited to the experience of the physician. The types of bacteria, which can cause infections presenting an abdominal abscess, are highly variable, further supporting the observations that damage to different regions of the intestine can result in vastly different types of infections. For example, patients suffering from a ruptured colon can become infected with intestinal gram-negative bacteria and/or anaerobic bacteria. Abscesses caused by *S. aureus*, *Pseudomonas* species and other nosocomial, drug-resistant bacteria can often occur in patients with abdominal drainage tubes. The most common pathogen-associated pleural cavity trauma-related infections are *S. aureus* related and these infections typically result from bacterial colonization of abrasions present on the patient's skin or contamination of indwelling devices. Contamination of indwelling devices with Gram-negative organisms should be considered, if pyothorax infections are secondary to sub-diaphragm infections.

19.1.1.3   Nosocomial Infections

Most patients suffering from traumatic injuries receive timely treatment in hospitals, including antibiotic prophylaxis and wound debridement. Therefore, any resulting infections are nosocomial, typically occur superficially and are generally easy to manage. Most infections of this nature develop within 48 h in hospital and are the most common type of infection observed in burn and trauma patients. Unfortunately, the rates of nosocomial infections continue to rise, in part due to the development of more invasive (and frequent) therapies, the misuse of antibiotics and iatrogenic contamination. Currently, nosocomial infections have seriously affected the quality of medical treatment, resulting in significant economic losses and wasted resources [2]. Although most burn and trauma patients are relatively young, the incidence of nosocomial infections is highest in this population since these types of injuries predispose patients to infections for the following reasons: loss of skin due to burns leaves an unprotected area vulnerable to infection by numerous pathogens, damage to the intestine can expose the body to flora not typically present in extra-intestinal tissues; treatment involves the use of indwelling devices that also provide a conduit for infectious pathogens; the use of conventional antibiotic prophylaxis may not prevent infections with virulent antibiotic resistant antibiotics and massive bleeding and serious damage may affect the host immunity. Respiratory and urinary tract infections are the most common sites of post-traumatic nosocomial infections, compared to wound

(incision infections), blood, chest and abdominal infections, which are rarer.

Nosocomial infections of burn and trauma patients can be caused by various pathogens, including gram-negative organisms such as *P. aeruginosa*, *E. coli*, enterbacteriaceae, crayresearch bacteria and gram-positive bacteria, including *S. aureus* and coagulase-negative *Staphylococci*. In addition, fungal infections caused by *Candida albicans* and other yeasts are also common. The rate of drug-resistant nosocomial infections is 91.6% and the rate of MSRA infections in burn and trauma patients was higher than in other in-hospital patient populations. Although nosocomial infections from different geographic locations vary in the context of the organisms most frequently identified, the group of pathogens associated with these infections remains constant worldwide.

The anatomic sites of trauma-related nosocomial infections vary with the nature of the injury. Minor injuries with an injury severity score (ISS) of 1 – 15 are typically UTIs (76.8%). Moderate injuries (ISS 16 – 25) are associated with higher incidence rates of respiratory infections (from 6.7% to 8%) and blood infections (from 1.5% to 41.7%). UTI infections in this group occurred at a reduced frequency (from 76.8% to 35%). Severe injuries (ISS 19) presented with even higher incidence rates of respiratory infections ranging from 51.9% to 41.7% and blood and UTI infections remained at 8% and 2.6%, respectively. In summary, mild injuries are associated with UTIs and moderate and severe injuries with respiratory and blood infections. It has been reported that blood infection rates in patients with serious wounds reached as high as 19%. Blood infections commonly were reported to occur 1-week post injury. In addition, since trauma patients often present multiple wounds, it is common for more than one site to become infected. Studies have shown that 58% of post-traumatic nosocomial infections may involve two or more sites, while single site infections accounted for only 42% of infections.

The nature of pathogens associated with nosocomial infections has similar distribution patterns in hospitals. For example, pathogens associated with respiratory infections in intensive care units (ICUs) are often the result of iatrogenic infections caused by respiratory pathogens. In addition, due to the ICU environment and the systemic use of antibiotics, many infections are caused by *Pseudomonas* species and *S. aureus*. Previous research has demonstrated that antibiotics can change a patient's normal intestinal flora by eliminating commensal populations and selecting antibiotic resistant organisms that are also typically pathogenic, including strains of *Pseudomonas* and other Gram-negative bacteria, including pathogenic *E. coli*, crayresearch bacilli and fungi.

Bacteria commonly associated with blood infections include *P. aeruginosa*, *E. coli* and coagulase-negative *S. aureus*. Bacteria isolated in the context of contaminated indwelling devices, such as catheters, include *S. aureus*, coagulase-negative *S. aureus*, *C. albicans* and intestinal bacteria.

Common wound infection-associated bacteria include coagulase-negative *S. aureus* and *Pseudomonas* species. In addition, the causative agents of wound infections are related to the type of injury sustained, that is, wound infections following severe trauma are more likely to be caused by intestinal pathogens such as *Acinetobacter* species, *Proteus* species, crayresearch bacteria and *Pseudomonas* species.

19.1.2   *Predominant Pathogenic Bacteria*

Predominant pathogenic bacteria associated with infections post-surgery or associated with trauma include Gram-positive cocci, Gram-negative bacilli, anaerobic bacteria and fungi. In addition, dysbacteriosis resulting from antibiotic use or the translocation of normal gut flora into extra-intestinal sites caused by biological barrier damage (resulting from either surgery or trauma) can lead to severe infections.

19.1.2.1   **Gram-Positive Cocci**

S. aureus and *Streptococcus* species are the predominant pathogenic bacteria associated with surgical procedures or trauma.

Staphyloccocus. A significant percentage of the natural flora of humans is comprised of *Staphylococcus* species. These organisms can colonize the upper respiratory tract and skin surfaces and are also the most common pathogens associated with post-surgical and trauma-related infections (primarily *S. aureus* and *S. epidermidis*). Many *S. aureus* isolates can produce hemolysins, leukotoxins, tissue destructive enzymes (such as hyaluronidase), T cell super antigens (such as toxic shock syndrome toxin I), B cell super antigens (such as protein A), immunomodulators (such as the MHC analog protein [Map or Eap] and the extracellular fibrinogen-binding protein [Efb]) and numerous antibiotic resistant determinants. These organisms are the most common pathogens associated with systemic blood-borne infections.

   S. epidermidis is also a predominant organism associated with the natural human skin flora and is responsible for numerous opportunistic infections associated with post-surgical procedures or trauma-related damage. *S. epidermidus* isolates secrete extracellular slime substance (ESS) which adheres to bacterial surfaces and interferes with cellular immune responses and prevents antibiotics from reaching the bacteria. Both *S. aureus* and *S. epidermidis* have acquired multiple antibiotic-resistance genes including methicillin resistance *i.e.* methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant *S. epidermidis* (MRSE). In addition, *S. aureus* has acquired the ACME element from *S. epidermidis* that facilitates the intracellular survival of *S. aureus*. This panel of virulence factors makes prevention and treatment of infections caused by these pathogens a significant health-risk priority.

Enterococcus. *Enterococcus* species are part of the normal intestinal flora of both humans and other mammals, and the prevalence of infections from these organisms are only second to *S. aureus* infections. In addition, Enterococcal infections are common causes of UTI and sepsis cases post surgery. Treatment complications are associated primarily with enterococcal strains that are resistant to a broad range of antibiotics.

Streptococcus. *Streptococcus* genera include 40 subtypes and these organisms are a part of the normal oral cavity and gastrointestinal flora. Not surprisingly, infections with these organisms are common agents of post-surgical or

post-trauma infections. Group A *streptococci* are some of the more virulent *streptococci*, in part due to their ability to produce numerous enzymes and exotoxins, including the M protein, hyaluronidase, streptokinase, streptodornase, streptococcal hemolysin and pyrogenic exotoxin. Streptococcal infections can be present as allergic diseases, infections resulting in heart valve and kidney damage, bacteremia, sepsis, septicopyemia or purulent infections.

19.1.2.2   Gram-Negative Bacilli

Gram-negative bacilli associated with post surgical infections typically are caused by *Pseudomonas sp*., *Escherichia sp*., *Klebsiella sp*., *Serratia sp*., *Proteus sp*., *Acinetobacter sp*., *Citrobacter sp.* or enterobacteriaceae.

Pseudomonas. *Pseudomonas sp*. is widely distributed in nature and comprises more than 200 species, some of which comprise members of normal human flora. Depressed immune responses associated with post surgical procedures and trauma, in addition to invasive treatment protocols (*i.e.* tracheotomies and the use of indwelling devices) lead to *Pseudomonas sp*. infections, making infections with this pathogen important to consider in the context of nosocomial infections. *P. aeruginosa* infections are the fourth leading cause of Gram-negative sepsis, and the leading cause of sepsis-related deaths. In addition, exposure to *Pseudomonas sp.* can easily progress into respiratory infections, infective endocarditis, UTI, central nervous system infections, digestive tract infections, joint infections and skin and soft tissue infections.

Escherichia. *Escherichia sp.* infections are primarily caused by different *E. coli* strains even though many non-pathogenic *E. coli* strains comprise a significant percentage of the healthy intestinal flora. Pathogenic *E. coli* have been divided into five primary categories: enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), enterohemorrhagic *E. coli* (EHEC) and enteroaggregative *E. coli* (EAEC). The most common infection route associated with these *E. coli* strains results from parenteral infections that are present as UTI and acute diarrhea. These types of *E. coli* infections are common post surgery and trauma.

Klebsiella. *Klebsiella sp.* is a Gram-negative bacilli comprising 7 strains that include *K. pneumonia*, the primary *Klebsiella sp.* associated with iatrogenic infections. *K. pneumonia* isolates have been demonstrated to produce extracellular toxic compounds (ETC, the primary [63%] capsular polysaccharide), lipid polysaccharide (30%) and small amounts of protein (7%). Some strains produce thermolabile (LT) and thermostable (ST) toxins and capsule formation is also related to pathogenicity.

Serratia. *Serratia sp.* is small, gram-negative bacteria which can produce water-insoluble yellow, purple and red pigments. *Serratia sp.* has been discovered in soil, water, plants and in animal and human intestinal tract and urinary tract samples. *S. marcescens* is the main nosocomial-associated S*erratia sp*., and infections with this pathogen are associated with pneumonia, sepsis, blood transfusion infections and surgical, postoperative infections and UTI.

Proteus. *Proteus sp.* is distributed widely in nature, including soil, water, and waste and in the intestines of humans and other mammals. *Proteus sp.* can be responsible for a variety of infections, including respiratory infections, diarrhea, UTI, peritonitis, otitis media, mastoiditis, infective endocarditis, meningitis, sepsis and food poisoning. Finally, Proteus infections are a primary cause of post-surgical and wound infections.

Acinetobacter. This genus can be divided into 6 species that are also widely distributed in external environments such as water, soil, and other damp environments. *Acinetobacter sp.* comprises 25% of the normal human skin flora of humans in addition to 7% of bacteria recoverable from pharynx (7%) cultures. In addition, it has been found to colonize the conjunctiva, gastrointestinal tract and has been identified in both saliva and vaginal secretions. Due to their adherence properties, these organisms are difficult to remove from medical instruments and are a primary cause of post-surgical iatrogenic infections and trauma. Their prevalence in clinical settings is only second to that of *P. aeruginosa*.

Enterobacter. *Enterbacteriaceae* in general comprise a group of pathogens that are widely distributed in nature and are members of the intestinal flora of both humans and other animals. *E. aerogenes* and *E. cloacea* are common causative agents of UTI and respiratory infections occurring post-surgery or trauma. Infections with these pathogens can progress to sepsis or meningitis.

Citrobacter. *Citrobacter sp.* exists widely in nature and is present in the intestines of both humans and animals under normal conditions. However, opportunistic infections caused by members of this genus typically manifest themselves as hemorrhagic enteritis and infections are common post-surgery and trauma.

19.1.2.3   Anaerobes

Anaerobes comprise a significant portion of the normal human intestinal flora and can also colonize human skin and the deep mucosa of the sinus tract. A feature that is characteristic of patients' post-surgery and trauma is tissue ischemia and local necrosis associated with low oxygen concentrations that make patients vulnerable to anaerobic bacterial infections. Most anaerobic bacteria are aerogenic, such as the tetanus bacillus and other *Clostridium sp*. Most sporeless anaerobic bacterial infections are often the result of endogenous strains of bacteria (*i.e.* autoinoculation) except for *C. tetani* infections. Infections caused by anaerobic bacteria are the result of mixed infections that include bacteroid (*Bacteroides sp*.) and digestive streptococci, often in combination with other bacteria such as *E. coli*. Furthermore, *B. fragilis* can produce a beta amide enzyme which significantly reduces the efficacy (and can even inactivate) penicillin-based antibiotics at the site of infection making the choice of antibiotic important. Anaerobic bacterial infections are often accompanied by a purulent smell. Furthermore, the growth of sporeless anaerobic bacteria is slow, therefore infections with these pathogens may not be present until later. For example, wound infections post surgery and trauma often appear several days after stitches are removed.

19.1.2.4   Fungi

Fungi are a type of eukaryotic microbial cell widely distributed in nature and can be considered opportunistic human pathogens in most cases. Pathogenic fungi are divided into shallow and deep fungi. The former mainly exists on skin, hair and nails and treatments to eradicate fungi from these surfaces are difficult, although these fungi do not generally pose a severe threat to human health. Infections with the latter, however, may result in systemic, splanchnic infections that may result in death. Fungi cause diseases in animals, plants and humans, including various types of infections and allergic diseases. Infections typically only occur following major surgery, severe trauma, in burn victims, patients with intestinal disorders or in immune-compromised individuals. Common fungal infections are caused by *C. albicans*, *Aspergillus sp.* or mucor fungi. The most common fungal infections are caused by *C. albicans* infections that are usually present as upper respiratory tract, oral cavity, vaginal or bowel commensal infections. Infections caused by *Aspergillus sp*. and mucor fungi are also responsible for serious post-surgery or trauma-related infections.

19.1.2.5   Viruses

Viral infection rates of post-surgery or trauma are lower than observed for either bacteria or fungi. Cytomegalovirus and herpes simplex virus infections have been reported post-surgery (mainly in children) and cytomegalovirus antibodies have been detected after surgery and trauma [3]. Cytomegalovirus inclusion bodies have also been seen in adult burn victims. However, blood transfusions post-surgery and trauma cannot be ruled out as the cause of the infections. Serious injury requiring significant amounts of transfused blood has also been associated with serum hepatitis and cytomegalovirus infections.

19.1.3   Primary Pathogenic Factors

Infection and the nature of disease presentation depends on various host-pathogen interactions. The arsenal of virulence factors associated with respective pathogens will greatly influence disease presentation. Factors that can influence colonization efficacy are adhesins that facilitate microbial adherence to host extracellular matrix structures (infections cannot begin without microbial attachment). In addition, receptors that bind to host receptors typically mediate pathogen internalization into host cells, facilitating immune evasion and causing damage to host tissues. Some bacteria produce capsules that are resistant to phagocytosis, while toxins and invasive enzymes can damage various tissues, including immune system components.

19.1.3.1 **Exotoxins and Invasive Enzymes**

Exotoxins and invasive enzymes secreted by some bacteria during the initial infection stages allow bacteria to create a protective niche facilitating bacterial reproduction. For example, *P. aeruginosa* exotoxin A can interfere with (mammalian) protein synthesis, resulting in toxic effects that can facilitate tissue destruction leading to gangrene, the formation of deep abscesses, hypotension, edema, hepatic steatosis, kidney hemorrhagic necrosis and death.

The *S. aureus* toxic shock syndrome toxin-1 (TSST-1) is a T cell super-antigen which ligates T cells to major histocompatability antigen II (MHC-II), expressing antigen presenting cells in a non-antigen specific manner resulting in polyclonal activation and deletion of up to 20% of T cells. As a consequence of this process, T cells release vast quantities of IL-1 and TNF, which results in fever, desquamation, rashes, osmotic imbalances, hypotension, multiple organ damage and shock. It also can increase the sensitivity of the host to endotoxins and alter capillary permeability resulting in cardiovascular disorders. In addition, *S. aureus* coagulase mediates fibrin clot formation, protecting *S. aureus* from immune clearance and access by antibiotics.

The streptococcal thermophilus toxin (SPE) is responsible for causing scarlet fever in humans and is associated with local or systemic roseola, fever, pain, nausea, vomiting and general malaise. *Streptococci* also produce hyaluronidase that hydrolyzes hyaluronic acid, resulting in tissue destruction associated with bacterial dissemination.

19.1.3.2 **Endotoxins**

Endotoxins, such as the gram-negative cell wall component lipid polysaccharide (LPS), can be released from the bacterial surface under normal physiological conditions. The chemical constituents of LPS include lipid A, polysaccharides and amino acids. Lipid A from different bacteria is similar; therefore different bacterial LPS molecules will have similar effects on human physiology. LPS is heat stabile, weakly antigenic and a potent immune-stimulator. LPS is the primary factor driving septic shock as a consequence of non-specific stimulation of macrophages, endothelial cells and granulocytes, stimulating the release of inflammatory mediators such as IL-1, TNF-α and IL-6. In addition, endotoxin can activate the alternative complement pathway and promote B lymphocyte proliferation. Endotoxemia post-surgery results in the systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS).

19.2   **Post-Surgery- and Post-Trauma-Related Wound Infections**

Infections have been the leading cause of death in both surgery and trauma patients, and surgical wound infections are one of the main complications

associated with these patients since these infection types severely affect wound healing, extend hospital stays, raise treatment costs and can result in severe and even fatal infections [4]. Due to the constant change in microbial virulence patterns and increased resistance to antibiotics, the incidence and severity of wound infections remain a problem that cannot be ignored in the treatment of surgery and trauma patients.

19.2.1   Etiology and Pathogenesis of Wound Infections

Surgery and trauma create significant damage to protective skin barriers, exposing subcutaneous tissues to environmental pathogens. Commensal skin flora and environmental opportunistic pathogens can invade surgical- or trauma-related wounds resulting in life-threatening infections. Although pathogens can be identified from all wound infections, not all organisms will necessarily cause disease in all individuals since many host (immune status, health) and pathogen-related factors (virulence factors) come into play during the infection process. However, the right combination of virulence factors in the context of an environment conducive to infection (surgery or trauma), combined with diminished host defenses, greatly increase the risk of developing a wound infection. Risk factors also associated with developing a wound-related infection are extensive antibiotic use and hormone therapies that will change the natural flora of both the skin and intestine, thereby increasing the risk of developing an endogenous infection. The formula for the risk of developing a wound infection described by Altemier *et al*. is as follows: the risk of wound infection = the quantity × toxicity of pathogens / host resistance.

19.2.2   Prevention and Treatment of Wound Infections

Wound infections are the most common complications associated with surgical and trauma patients. In China, surgical wound infections accounted for 13% – 18% of inpatient cases. In mild cases, postoperative infections increased pain and hospital stays by about 10 days, resulting in significant increases in health care costs. In serious cases, postoperative infections led to surgical failure and in some cases death.

Since the causes and anatomical location of wound infections vary, so does clinical presentation. If the wound results from a surgical incision, the wound should be relatively clean. However, wounds caused by non-sterile objects may lead to infected necrotic tissues, hematomas and foreign body infections. Open fracture wounds are often associated with different degrees of tissue injury and are more prone to infections. Once the infection develops, treatment becomes more difficult, especially in cases of traumatic osteomyelitis which may affect limb recovery time and function, leading to physical disabilities and potential

life-threatening infections [5].

19.2.2.1 Wound Infection Prevention

Expedient surgical debridement is important in preventing wound infections and is the most effective measure in reducing wound infections. Debridement not only prevents infections, but also creates an environment conducive to the repair and healing of deep tissues and in the restoration of function and structural integrity of the injured area. The process of debridement includes the removal of necrotic tissue, hematomas and/or foreign bodies while retaining viable tissues. The beneficial effects of debridement are more effectively observed if this process is carried out no later than 6 – 8 h post injury, since bacteria during this time frame have not yet penetrated into deeper tissues of the contaminated wound. For smaller wounds resulting in less serious injuries contamination is less likely and less severe, particularly in cooler climates. Smaller wounds can be sutured 24 h post injury if they are correctly cleaned. For severely contaminated wounds, debridement is more difficult 24 h after injury and in warmer climates debridement must be carried out quickly to prevent pathogen dissemination. Studies have demonstrated that repeated debridement every 48 – 72 h is important in the removal of necrotic tissues not removed following the initial debridement procedure. Full thickness wound resection, followed by a second resection, are the most effective debridement procedures. For some wounds, which may not have been completely resected all at once, should be repeatedly washed to remove all contaminants prior to continuing with the resection process. Open fracture wound closures should be carried out as soon as possible to reduce infection rates since avoiding dehydration of deep tissues will accelerate fracture healing.

Wound debridement should be considered, based on the degree of wound contamination, size and depth. In general, primary sutures should only be put on clean wounds no more than 12 h post debridement. Large and deep wounds require drainage after primary suture. For wounds in tissues with a rich blood supply (head, neck and face), it is important that sutures are not made until thorough debridement is carried out, even if it means that the injury will take longer to heal. Primary sutures put in after debridement are important in protecting wounds from infection and environmental contaminants. However, for seriously contaminated wounds of soft tissues, or tissues where efficient debridement cannot be performed, primary sutures are not recommended and should not be put in until the wound can be better stabilized. In addition, high impact-induced soft tissue contusions or lacerations generally do not require primary sutures due to the inflammation at the injury site. In summary, sutures should be utilized to stabilize wounds following debridement procedures.

In dealing with wound treatment, the systemic application of antibiotics, especially when used prophylactically, remains controversial and the utilization of antibiotics in surgical procedures has become more widely spread. In order to prevent the development of postoperative wound infections, prophylactic

utilization of antibiotics has become routine even though postoperative infections have not been reduced. However, antibiotic use has had some beneficial effect on preventing wound infections not associated with surgical procedures. However, the overuse of antibiotics and the utilization of the incorrect antibiotic type does not only fail to achieve the desired effects but results in increased side effects and in the selection of resistant strains.

Prophylactic antibiotic use for the prevention of wound and/or surgical infections does have merit but must be carried out appropriately, that is the respective antibiotic used must be applied in the correct dosage and for an amount of time conducive to bacterial clearance or, in the case of surgical prophylaxis, at levels shown to prevent bacterial contamination [6]. Antibiotics should be administered intravenously at a rate that ensures that the correct antibiotic concentration is achieved in blood and tissues. If necessary, antibiotics can be administered during surgical procedures and the antibiotics selected should be used short-term and not utilized post-surgery. Some researchers believe that a single dose of antibiotics can be used to treat purulent *S. aureus* infections when combined with debridement, irrigation and primary sutures. However, systemic antibiotic use is unnecessary following wound closure, particularly since antibiotic use at this juncture will result in microflora imbalances and will select antibiotic resistant organisms without reducing wound infection rates. Early use of antibiotics for the prevention of infections associated with open fractures, however, is well accepted. Studies have indicated that bacterial contamination of open fracture wounds likely occurs within the hospital environment and early use (3 – 5 days) is recommended prior to treatment. Lee *et al*. reported that positive rates of bacterial cultures from fracture wounds were not high before debridement, are not predictive of infection nor did they reflect the species of bacteria that may be the causative agent of an infection (if it develops) [7]. In summary, repeated, thorough debridement is key to preventing wound infections and even prophylactic antibiotic use cannot replace debridement as the primary anti-infective strategy prior to suture use.

19.2.2.2 Treatment of Wound Infections

Effective clinical diagnosis and treatment of wound infections is needed to prevent systemic disease and permanent tissue damage. Wound infections are generally characterized by inflammation, redness, heat, pain, and when pus is present it is indicative of an infection. Cellulitis around the wound is more common. In addition, persistent tissue necrosis around the wound is another sign of wound infection. A key first step to wound infection treatment is thorough pus drainage. Mechanical removal of fibrin deposition and bacterial debris is critical to the healing process. Typically, these procedures are sufficient and do not require the systemic use of antibiotics, assuming that wound treatment is initiated in a timely manner. However, more serious cellulitis or persistent necrosis of the surrounding tissues will necessitate the use of antibiotics, fluid replacement therapy and supportive therapy (following debredment) [8].

Two severe soft tissue infections must be considered separately due to their severity.

Acute necrotizing fasciitis. Acute necrotizing fasciitis is a form of severe subcutaneous tissue and fascia necrosis accompanied by severe systemic symptoms [9]. The most common cause of this form of infection is trauma, especially deep penetrating wounds that physically localize microorganisms to the fascia surface where there are reduced numbers of blood vessels surrounding the muscle bundles of the fascial spaces. Therefore, proliferating microorganisms can spread rapidly at the fascia surface, sometimes resulting in fascia necrosis. Surgical contamination of hollow organs as a result of inappropriate antibiotic use and serious primary suture infections can often result in necrotizing fasciitis. Infections resulting in necrotizing faciitis are the result (in most cases) of mixed infections comprised of both aerobic and anaerobic bacteria resulting in the production of fetid pus production. Rea and Wyrick confirmed the presence of gram-positive bacteria (including *Streptococcus* and *S. aureus*), gram-negative bacteria and anaerobic bacteria in necrotizing faciitis tissues. The most prominent clinical manifestations of disease are fascia necrosis, cellulitis, edema, skin discoloration and gas gangrene. Symptoms associated with disease onset include (at the site of infection) reddening, inflammation, heat, pain and rapid dissemination of the infection. Severe cases can result in sepsis, toxic shock and death.

Necrotizing faciitis cases are not common but are progressing rapidly. An additional complication is that early symptoms are not necessarily indicative of the severity of the infection that can result in a delayed diagnosis that in turn leads to higher mortality rates. The most important parameter in recognizing the symptoms of early necrotizing faciitis is physician awareness. Extensive necrosis of subcutaneous fat and fascia and subcutaneous, tunnel-like changes in the absence of muscle involvement (early) are important diagnostic signs. Cellulitis with hemorrhagic spots on the skin are mostly a consequence of group A streptococcal infections. The main manifestation is severe pain that can be caused by gentle palpation of the wound site, with pain extending to the edge of trauma areas. Cases may present little or no purulent secretions but systemic symptoms are more serious than those at the wound site. Bacteriological examination of pus smears is important in diagnosis.

Early debridement and drainage are key to the treatment of this infection type, including complete removal of necrotic tissues followed by repeated debridement and drainage as needed. The use of antibiotics is based on bacterial diagnosis from smear results initially, followed by modifications following more sensitive bacterial culture and antibiotic sensitivity testing. Fluid replacement therapy and nutritional support are provided as necessary.

Clostridium muscular necrosis (gas gangrene): Clostridium muscular necrosis (gas gangrene) is a rapid developing, severe, acute infection caused by infections with *Clostridium perfringens*; a gram-positive, short and thick spore-forming anaerobic bacteria. This type of infection is common following severe trauma, especially in patients with open fractures, significantly contaminated muscle wounds and infections in tissues with poor blood circulation. In addition,

abdominal surgery may lead to Clostridium muscular necrosis, due to cross-infections or endogenous infections typical of intestinal surgery. *C. perfringens* may disseminate to deeper tissues following stab wounds or other injuries to deeper tissues resulting in gas gangrene. The incubation period of this infection is shorter, *i.e.* 3 or more days after injury is common. Wound pain is one of the first symptoms to present itself and is severe and difficult to control. Edema develops around the wound site and the skin becomes pale, shiny, rapidly turns purple and finally turns a dark gray, accompanied by the emergence of large and small blisters containing foul-smelling serous or blood liquid. Crepetation can be heard following palpation of most soft tissue infection cases. Due to deep compartment infections, limbs can be lost in a short time period. In addition, severe systemic manifestations can present themselves as a consequence of exotoxin production.

Gas gangrene diagnosis is usually not difficult, but physicians need to remain vigilant to diagnose this type of infection. Early diagnosis and treatment are critical not only to rescue affected limbs but also to the patient's life. Palpable crepetation around the wound, gas discernable in muscle X-ray and thick gram-positive staining of secretion smears are the main diagnostic criteria. Once disease is diagnosed, it must be treated actively and rapidly to control the infection.

Due to the rapid progression of necrotizing fasciitis, timely and extensive debridement is needed to remove necrotic tissues and foreign bodies. Systemic antibiotic therapy is also recommended and hyperbaric oxygen therapies may be used as surgical adjuvant therapy.

19.3   Intra-Abdominal Infections Associated with Surgery and Trauma

Intra-abdominal infections result from significant damage to the host's abdominal cavity caused by the invading microorganism. Intra-abdominal infections resulting from surgical trauma, also known as surgical intra-abdominal infections, are infectious diseases of the abdominal cavity developing after abdominal surgery or trauma and requiring surgical interventions as part of the treatment process. Intra-abdominal infections are caused by gut flora (most commonly *E. coli* and anaerobic *Bacteroides sp*.) often present with suppuration and necrosis resulting in the destruction of the intestinal architecture and needing surgical treatment such as incision and drainage or puncture and drainage as part of the treatment process.

19.3.1   Acute Peritonitis Resulting from Surgery and Trauma

Peritoneal cavity infections represent the most important complication associated with intra-abdominal infections and are also the most difficult to diagnose and

treat. Trauma, combined with intra-abdominal infections is commonly observed in the gastrointestinal tract, biliary tract, bladder and other hollow organs. Abdominal infections post-surgery develop as a consequence of colon content leakage, leakage of GI tract anastomosis, biliary or pancreatic leakage or perforations to the colon due to endoscopic procedures. Because there are a small number of bacteria within the stomach and duodenum, the incidence of severe intra-abdominal infections is low when injuries occur at these sites. However, the incidence of intra-abdominal infections is relatively high, due to the large amounts of intestinal bacteria in the distal gut ($>10^{10}$/g of feces in the colon and rectum).

Pathological changes associated with peritonitis developing post-surgery and trauma depend on the bacterial species present, its concentration, virulence, host immune status and how rapidly treatment is administered. For patients with intestinal rupture, the longer the operation time the greater the likelihood of bacterial dissemination within the abdominal cavity.

Intra-abdominal infections are multi-bacterial in nature, comprised of aerobic and anaerobic bacteria. Most strains belong to bacteria common to the human intestinal tract, and skin. *E. coli* is the dominant aerobic bacteria, and *B. fragilis* the dominant anaerobe associated with these types of infections. Infections caused by gram-negative bacilli are more common following surgery of the GI tract and pathogenic bacteria associated with infections of the spleen or pancreas are mainly caused by *staphylococci.* Bacterial virulence and pathogenicity resulting from mixed infections can be significantly increased as a consequence of bacterial synergy. Aerobic bacteria utilize oxygen from the surrounding environment, making the environment conducive to anaerobic bacterial growth. In turn, anaerobic bacteria release enzymes, growth factors and host response inhibitors that facilitate survival and propagation of aerobic bacteria. In addition, aerobic bacteria also provide vitamin K used for growth and reproduction of anaerobic bacteria. Furthermore, mixed infections reduce the efficacy of antibiotic therapies.

When non-virulent bacteria are introduced into the abdominal cavity of an immunocompetent host, post-surgical and post-traumatic peritonitis is transient. Intra-abdominal abscess formation is a sign of localized inflammation associated with bacterial clearance or control of the infection and will only form when the bacterial concentration present in the abdominal cavity is too large to be cleared by the body's defenses.

Fever, with or without chills, may be the only manifestation of abdominal infections. Some gram-negative bacterial infections may only be present with a low-grade fever, with maximum temperatures in the afternoon or evening. Pain may be helpful in determining the site of infection. However, pathogen characterization will require bacterial culture of drained samples or pus, using methods conducive to the growth of both aerobic and anaerobic bacteria.

Prompt repair of the wound and closure of the damaged intestinal tract and the immediate use of broad-spectrum antibiotics capable of clearing both aerobic and anaerobic bacteria may be effective in preventing or reducing post-traumatic acute peritonitis.

Correct surgical procedures are critical to the prevention of infections resulting from colon injury. Adopted surgical methods that can affect the outcome include

fecal bypass procedures that depend on the type of wound, severity, patient health, how long the wound has been open, the extent of the intra-abdominal infection, combined injury to other organs, shock and the technical level of the surgeon. Clinical treatment should be individualized. For example, if a patient is generally in good health, primary surgical resection should be adopted. In addition, regardless of the type of surgery, immediate closure of the rupture is imperative, followed by thorough debridement, early full washing and postsurgical drainage. Close attention must be paid to anastomosed regions, especially to pressure and blood supply. The importance of emptying the bowel cannot be ignored. Because preoperative bowel preparation cannot always be carried out prior to emergency surgery, it is important to carry out a complete GI decompression and bowel irrigation. Additionally, omentum or fat can be used to cover respective anastomosis to reduce the incidence of anastomotic leakage. In order to reduce blood clots, thorough and repeated washing of the abdominal cavity with the right temperature saline solution during the operation is needed to remove foreign bodies and reduce the number of bacteria present.

19.3.2   Intra-Abdominal Abscesses after Surgery and Trauma

Intra-abdominal abscess formation, including subphrenic abscesses, pelvic abscesses and interbowel abscesses are comprised of a localized accumulation of liquor puris in the abdominal cavity due to liquefaction necrosis of surrounding tissues such as the bowels, viscera, the abdominal wall, omentum or mesenterium. Intra-abdominal abscesses often occur after abdominal surgery and trauma. X-ray and radionuclide scanning are helpful in their diagnosis and BUS and CT scans can accurately locate the majority of abscesses and guide the puncture and catheter drainage procedures. The pathogenic bacteria associated with abdominal abscess are different and typically abscesses are comprised of intestinal gram-negative bacilli and obligate anaerobes that are sensitive to conventional antibiotic therapies. Some intra-abdominal abscesses in patients with intra-abdominal drainage tubes can be caused by staphylococci. *Pseudomonas sp.* and other drug-resistant bacterial strains associated with other nosocomial infections can also lead to intra-abdominal infections following long-term use of antibiotics. The identification of pathogenic bacteria is dependent on bacterial culture.

In order to prevent postoperative intra-abdominal infections and abscess formation, preventive measures need to be in place and include careful surgical procedures, protecting the surgical field, preventing and reducing endogenous bacterial contamination. Bacteria can be cultured from the abdominal cavity if surgical procedures are too long and the abdominal cavity is exposed to environmental contaminants during this time. Antibiotics should be administered before surgery to ensure adequate antibiotic concentrations in tissues.

Treatment of intra-abdominal abscesses includes nutritional support, antibiotic therapy and adequate drainage. Intra-abdominal abscesses may be absorbed by the body if early antibiotics and supportive therapy are administered. BUS super-

positioning puncture and drainage are simple and effective treatments for a subphrenic abscess, deep abscess and small abscess filled with thin pus. However, surgical drainage is applicable for an abscess with large cavities, thick-walls and/or multilocular.

19.4   Enterogenic Infections Associated with Post-Surgery and Trauma

Large numbers of clinical studies have shown that enterogenic infections are the most common endogenous infections associated with surgery and trauma. Enterogenic infections are not only associated with the development of refractory shock caused by severe trauma and refractory sepsis, but also play an important role in the pathogenesis of MODS.

Humans are colonized on their skin, genitourinary tract, GI tract, oral cavity and lung epithelial surfaces by a myriad of different types of bacteria that constitute the normal flora. The nature of this flora has evolved with humans and serves various beneficial purposes at respective anatomic sites. The quantity of microorganisms comprising the human intestinal flora is larger than that in any other organ in the body and the number of bacteria (10^{14}) is 10 – 20 times the number of human cells comprising the human body. Intestinal microflora form a biological intestinal barrier that protects the intestinal epithelium from colonization with pathogenic bacteria, participates in host metabolic processes and contributes nutritional value that promotes (host) growth and health. In 2001, Hooper *et al*. found that the major human intestinal bacteria formed part of the host biological and immune barriers that contribute to intestinal growth, symbiotic bacterial metabolism, nutrient absorption and angiogenesis. Therefore, the balance and health of the intestinal microflora is a sign of health. The functional integrity of the normal intestinal flora (and the intestinal barrier they provide) has an important role not only in preventing bacterial infections, but also in diminishing inflammation, ulcer formation and preventing allergic and neoplastic diseases.

When the intestinal barrier function is impaired, intestinal bacterial translocation can occur. The currently accepted view is that bacterial translocation is the process by which microorganisms and their respective toxins cross the intestinal wall into otherwise sterile tissues, including the mesenteric lymph nodes, portal vein and other distant organs or systems, providing primary bacterial foci that contribute to various infections. Following surgery and trauma, the intestinal barrier function can be impaired due to shock, hypoxemia, malnutrition and reduced immune function which facilitate intestinal flora translocation leading to intestinal infections. Therefore, understanding the structure and function of the intestinal barrier will help with the control of intestinal infections.

19.4.1 Intestinal Barrier Function

Intestinal barrier function indudes structural basis of the intestinal barrier and intestinal barrier dysfunction.

19.4.1.1 Structural Basis of the Intestinal Barrier

The intestinal barrier is comprised of mechanical, chemical, biological and immunological barriers. This complex barrier system effectively limits invasion of intestinal flora into extra-intestinal sites and constitutes an extremely important part of the body's defense system. Intestinal barrier integrity is an important factor in preventing bacterial or toxin translocation out of the intestine, although some degree of bacterial translocation constitutes the normal physiological process and plays an important role in the formation and maintenance of intestinal and systemic immune systems.

Mechanical barrier. This barrier consists of intestinal epithelial cells, tight junctions and plaque. The intestinal mechanical barrier is effective in preventing deep penetration of bacteria into mucosal tissues and establishes the physical architecture of the intestinal barrier. The intestinal epithelium consists of cells associated with gut absorption, goblet cells, Paneth cells and some endocrine cells. Gut absorption takes place on luminal surfaces and adjacent cells are connected by junctional complexes including tight junctions, gap junctions, adhesion junctions and desmosomes. Tight junctions are the most important type of cell-to-cell connection and can be of two types: (i) Villus epithelial tight junctions which have a smaller pore size and complex structure allowing only water molecules and other small molecules to selectively pass between cells; (ii) Duct cell tight junctions which have larger pore sizes and are simple in structure, allowing larger molecules to pass between cells. Tight junctions form a narrow band structure located outside of the top of the epithelial cell membrane. Adjacent cells form a fusion or match point, connected to form a continuous fishing-net-like structure. There are many proteins involved in the formation of tight junctions, including structural proteins (*e.g.* occludin, claudin, and JAM) and regulatory proteins (*e.g.* E-cadherin, actin, myosin, and cingulin). Tight junctions not only maintain cell polarity, but also selectively modulate the passive transfer of ions and macromolecules, forming a physical permeability barrier that limits bacterial and bacterial product transfer, making tight junctions important intestinal mechanical barrier components.

Chemical barrier. This barrier is comprised of intestinal mucus secreted by intestinal epithelial cells and a variety of digestive and intestinal digestive enzymes mediating various chemical reactions. Mucus lubricates the intestinal mucosa and protects it against mechanical and chemical injury. Glycoproteins and glycolipids secreted by intestinal goblet cells can be combined with bacteria, so that bacteria are discharged with intestinal fluid under the force of fluid flow. Lysozyme cleaves gram-negative cell-wall peptidoglycan bonds resulting in

bacterial lysis. Bile can combine with endotoxin to form detergent-like complexes that prevent endotoxin absorption through the intestine and cholic acid can degrade endotoxin molecules. Secretory IgA (SIgA) present in bile can opsonize bacteria preventing their attachment to epithelial surfaces. These broad-ranging components are important members of the intestinal barrier system.

Biological barriers. The GI tract is sterile in fetuses and following exposure to the external environment after birth the neonatal intestine becomes colonized *via* the oropharynx which then leads to GI tract colonization which is also exposed to microbes present in food. The small intestine and the colon are the last intestinal components to become colonized. Bacterial growth and reproduction in the colon establish an important intestinal biological barrier. Intestinal flora under physiological conditions remain relatively stable and the intimate interactions of the various bacterial populations between themselves and the intestinal epithelium create a physiological bacterial barrier consisting mainly of intestinal anaerobic bacteria combined with intestinal mucosa that prevents colonization with potential pathogens. However, the use of broad-spectrum antibiotics can cause bacterial imbalances, tipping the scale in favor of antibiotic-resistant pathogens not part of the normal flora. In summary, the normal flora maintains a dynamic balance in the intestine by preventing colonization with pathogens (contact inhibition), competing with pathogens for nutrients and producing bacteriocin and other anti-microbial factors.

Immunological barrier. This barrier is comprised of the intestinal immune system that neutralizes pathogenic bacteria and their products *via* cellular and humoral responses. Lymphocytes comprise one of the primary effector cell types of the immune system and the body's largest lymphoid tissue, the intestinal mucosa-associated lymphoid tissue (MALT), is situated in the gut. There are two different intestinal lymphocyte phenotypes: intestinal intraepithelial lymphocytes (iIEL) scattered throughout the intestinal epithelium and submucosal tissues rich in lymphocytes. Peyer's patch lymph nodes are another important lymphoid tissue. The cavity surface of Peyer's patch lymph nodes is covered with follicular epithelium which constitutes a single-cell complex comprised of columnar epithelial cells, goblet cells and microvilli. This complex forms lymphoid follicles under the epithelium. SIgA is the major intestinal immunoglobulin. The main function of SIgA is antigen binding that prevents antigens from passing through the intestinal mucosa. In addition, intestinal mucosal cells may also secrete IgE, IgM and IgG that are also important in mediating humoral immunity in the intestine.

Intestinal barriers made up of mechanical, chemical, biological and immune barriers that are key to host defenses against intestinal bacteria and endotoxin translocation. Any structural changes to these barriers are likely to lead to intestinal barrier dysfunction resulting in bacterial translocation.

19.4.1.2   Intestinal Barrier Dysfunction

Understanding the complexities associated with intestinal dysfunction can be

extrapolated from understanding intestinal failure, a concept proposed by Irving in 1956. Intestinal failure was defined as 'the overall reduction of functional gut, unable to digest and absorb food' as was observed in patients with short bowel syndrome (SBS). In 1981, Fleming and Remingtor stated that 'it was hard to maintain intestinal minimum needs of digestion and absorption of nutrients as the intestinal function fell'. In 1986, Carrico stated that 'the gut is the start organ of multiple organ failure'. In 1992, in the diagnosis criteria of multiple organ failure, Deitch established standards of intestinal injury, namely, bloating and food intolerance for more than 5 d and that the standard of failure should be stress ulcers and acute cholecystitis. In 1996, Wilmore proposed that the intestine is one of the primary organs affected in patients under stress and, in 2001, Nightingale stated that 'due to the reduction of intestinal absorption, supplementation of nutrition and water, electrolytes are needed to maintain health and (or) growth'. Although nearly 50 years have passed, our understanding of the intestinal function is still limited to the processes of digestion and absorption. In the 1980s, the basic understanding of the intestinal function was its role in food digestion, nutrient absorption and GI hormone secretion. When the body is under stress, the gut is in 'hibernation'. During shock, intestinal blood is redistributed to the liver, lungs, kidneys and other organs. In the 1970s, when our understanding of 'multiple organ failure' began to be better defined, there were no established criteria for defining intestinal failure. During the 1980s, it was noted that burn victims not suffering from wound infections could have bacteria recoverable from the blood. Furthermore, these bacteria were derived from the intestine and described as an 'enterogenic infection'. It has been confirmed in animal experiments that the intestinal mucosa has barrier function properties and that hypoxia and ischemia can impair the intestinal mucosal barrier function, defined by bacterial and endotoxin translocation into the lymph or blood circulation [10]. This phenomenon can be observed in animal models but in the human body it is still difficult to obtain direct proof. However, many recent reports indirectly confirmed the existence of intestinal bacterial and endotoxin translocation in the human body. Surgical procedures or illnesses contributing to the development of intestinal hypoxia and ischemia are associated with gut mucosal barrier dysfunction resulting in bacterial translocation associated with SIRS and sepsis that can progress to MODS.

Attention must be paid to complications associated with endotoxin and bacterial translocation that can result in MODS or facilitate endogenous infections (bacterial, fungal infections). Intestinal function definitions are no longer limited to descriptions of digestion and nutrient absorption, but also include descriptions of the intestinal barrier function. It has therefore been suggested that the definition of intestinal dysfunction should be 'the damage of intestinal substance and (or) intestinal function, resulting in the serious disorder of digestion and absorption of nutrients and (or) barrier'. It is involved in the patho-physiological changes of the body under stress and considered 'the central organ of body stress', 'the motor of multiple organ dysfunction'.

It is generally understood that the intestinal barrier function describes the intestine as preventing bacterial translocation into the body from the intestinal

lumen. In recent years, a large number of studies on the epithelial barrier function were performed. It has been widely believed that ischemia and hypoxia-induced bowel dysfunction are associated with intestinal necrosis. Under conditions of bowel dysfunction resulting from malnutrition, atrophy of the intestinal mucosa can occur and the villi height decreased. Intestinal permeability can be defined using the L/M (mannitol/lactulose) test that allows physicians to determine whether damage to the intestinal epithelial barrier has occurred. Although the clinical importance of maintaining an adequate intestinal barrier function is better appreciated today, further study is needed regarding mechanisms mediating this process that will allow for earlier diagnosis of gut barrier dysfunction.

To date, clinical definitions and methods of monitoring the intestinal barrier function are not well established. Indirect methods of monitoring the intestinal barrier function are widely used however, and include determination of intestinal permeability to macromolecules to indirectly confirm bacterial translocation. Clinical measurements of intestinal permeability to macromolecules can be carried out using a variety of water-soluble probe molecules that cannot be metabolized, can partly pass through the mucosal barrier and are quickly recoverable in urine. Commonly used molecular probes include PEG400 (5.3Å), mannitol (6.7Å), rhamnose (8.3Å), lactulose (9.5Å), cellobiose (10.5Å), ^{51}Cr-EDTA (11Å), 99mTc-DPTA (11Å). PEG400, mannitol and other small molecules can directly pass through villus epithelial tight junctions. Data derived from using these probes were used to estimate villus epithelial tight junction permeability. Lactulose, 99mTc-DPTA and other large molecular probes are mainly absorbed through duct cell tight junctions and the recovery of these probes is a reflection of duct cell tight junction permeability. Combined use of small and large molecular probes, such as the dual-sugar method M/L ratio method can be used to assess the permeability of two types of tight junctions. In recent years, "Pulsed Electrochemical Detection in High Performance Liquid Chromatography (HPLC-PED)" represents the most advanced method of measuring M/L permeability. Studies have shown that the M/L ratio correlated with the degree of trauma. In recent years, reports have also demonstrated that serum D-lactate and diamine oxidase (DAO) concentrations reflected intestinal barrier permeability. The using Chamber is another instrument used for studies assessing intestinal drug absorption and intestinal barrier function and is considered the most effective and direct advanced equipment to monitor the electrophysiological changes occurring in intestinal mucosal cells.

19.4.2   *Intestinal Barrier Function and Bacterial Translocation*

Intestinal bacterial translocation does not always result in a state of pathology. Data show that bacteria can be found in the mesenteric lymph nodes of healthy individuals with incidence rates of 5% – 10%. Limited bacterial translocation is likely to be a normal physiological process associated with luminal antigen processing by the MALT as a means of regulating immune responses against

luminal antigens. Under pathological conditions, significant bacterial translocation may likely cause a series of patho-physiological changes and sepsis.

It has been hypothesized that bacterial translocation is most likely to take place across ileal and colonic epithelium. However, it was recently demonstrated that bacterial translocation rates were equal in the jejunum, ileum and colon using ^{14}C-labeled *E. coli*. This study also demonstrated that bacteria translocated from the jejunum were more likely to survive.

Intestinal flora that colonized epithelial mucosal surfaces makes it difficult for pathogenic bacteria to colonize and translocate. Once the micro-ecological balance is disrupted as a consequence of antibiotic use or intestinal obstruction, however, the dominant bacterial population (usually gram-negative bacteria) may breach the mucosal barrier and translocation is then likely to occur. The most common bacteria associated with translocation are aerobic bacteria such as *E. coli*, *Klebsiella sp*. and *Proteus sp*.

Typically, bacterial translocation occurs after damage to the mucosal mechanical barrier takes place, in which case bacteria move from the mucosal layer into the tissue, adhere, colonize and translocate. If mucosal integrity is maintained, bacteria entering the peritoneum do so *via* endocytosis, followed by transfer by subepithelial macrophages to mesenteric lymph nodes where they are exocytosed. Bacteria not killed in macrophages by this process are free to elicit peritoneal infections. The functional status of macrophages, as carriers of bacteria, is considered to exert influence on bacterial translocation. However, in cases of trauma, shock or stress, the situation is different. Due to ischemia (reperfusion injury), the mucosa can suffer varying degrees of damage, including micro-structure changes and cell tight junction damage which are exploited by bacteria in the translocation process leading to infection. Bacterial endotoxins can more easily pass through the mucosal barriers compared to whole bacteria, so bacterial translocation as a result of stress is often accompanied by endotoxemia which in turn causes further damage to mucosal barriers and further increases mucosal permeability facilitating bacterial translocation.

However, endogenous bacterial translocation does not mean infection will develop since this process can be still impeded by the intestinal immune barrier. The induction sites of the immune barrier include the GALT (gut associated lymphoid tissue), MALT, isolated lymph nodes and the appendix. Immune effector sites include the intestinal lamina propria and intraepithelial lymphocytes. Intestinal tract-derived antigens can reach resting B cells present in the lymph nodes which in turn can migrate (via the lymphatic circulation) to the mesenteric lymph nodes and thoracic duct where they can in turn take up residence in the intestinal lamina propria. This process results in the production of IgA-positive B cells that continue to expand and differentiate into mature IgA-positive plasma cells that produce polymeric IgA that can in turn be translocated to luminal surfaces in the form of SIgA. SIgA can also be released into the intestine in bile. Antigen-specific SIgA can then opsonize bacterial targets forming antigen-antibody complexes that prevent adhesion and invasion of intestinal epithelial cells.

T lymphocytes can also differentiate and mature in response to intestinal

antigens. Mature CD4^{+} T cells make up a considerable percentage of lamina propria lymphocytes and CD8^{+} T cells make up 5% – 15% of the intestinal epithelial cell barrier, producing a series of cytokines that include IL-2, IL-6, TGF-α, TNF-α, and IFN-γ which help prevent bacterial translocation. However, under conditions of severe traumatic stress, chemotherapy, radiation therapies or local or systemic immune suppression, large numbers of bacteria will break through the intestinal barrier, translocate into blood and distant organs causing intestinal infections resulting in MODS. MODS in turn increases damage to the intestinal mucosa, further increasing bacterial translocation thereby feeding a vicious cycle.

Intestinal infections have their own characteristics in that they are primarily caused by bacteria normally colonizing the human body, and infections are caused primarily by anaerobic and aerobic mixed infections (with a higher proportion of anaerobic bacteria).

19.4.3 Clinical Manifestations of Enterogenic Infections

Intestinal bacterial translocation into mesenteric lymph nodes, portal circulation and other distant organs or systems is a gradual process that occurs as follows.

19.4.3.1 The Sub-Clinical Infection Stage

Bacterial translocation limited to the mesenteric lymph nodes results is in a stalemate. Infection does not typically develop or clinical manifestations are not obvious although fever may occur.

19.4.3.2 Septic Stage

As the bacteria break through the local defense barrier of mesenteric lymph nodes, pathogens continuously secrete toxins or endotoxins that are released into the circulation, stimulating systemic cytokine responses. If untreated, the resulting cytokine storm results in septic shock accompanied by respiratory distress. At this time point bacteria have not yet entered into the circulation and blood cultures are negative for bacterial growth.

19.4.3.3 Bacteremic Stage

In this stage, bacterial containment fails and bacteria break through all barriers into the blood, resulting in culture-positive blood cultures. This comprises the late stage of enterogenic infections.

19.4.3.4 SIRS or MODS Stage

Systemic inflammatory responses result as a consequence of severe infections characterized by body temperatures > 38 ℃ or < 36 ℃, heart rate > 90 beats/min, respiration rates of > 20 times/min or $PaCO_2$ < 4.3 kPa (32 mmHg), white blood cell counts > 12×10^9/L or < 4×10^9/L or immature neutrophils > 10%. MODS can be simultaneous or sequential, *i.e.* dysfunction of two or more organs at 24 h after serious infection or trauma. MODS is the most serious pathological process and the final outcome.

19.4.4 Prevention and Treatment of Enterogenic Infections

Clinically, it is important to maintain and improve intestinal mucosal permeability and barrier function and to prevent intestinal infections resulting from bacterial translocation. Intestinal integrity can be maintained by improving oxygen supply and blood flow to affected areas to meet the metabolic needs of respective tissues, prevent intestinal bacterial overgrowth using selective intestinal decontamination methods, maintain intestinal integrity by means of maintaining enteral nutrition and maintaining the gut microflora balance *via* probiotic use [11].

The intestinal mucosa is particularly sensitive to hypo-perfusion due to its high metabolism and capillary structure. After low blood volumes are corrected, decreased GI blood flow and visceral vascular contractions will continue for some time. The effect of adrenalin or other vasoactive drugs on intestinal perfusion is not clear; visceral vascular responses in individuals also vary significantly. During sepsis and SIRS, cardiac output is not representative of visceral blood flow. Visceral tissue perfusion can be re-distributed by administering vasoactive drugs. Despite improvements to the blood flow, there may still be a shortage of local perfusion. In general, increased cardiac output can increase visceral blood flow in patients with no impaired vascular regulatory mechanisms. Therefore, small doses of dopamine can then be used to improve visceral blood flow. In addition, improving intestinal mucosal perfusion also improves metabolism and further reduces intestinal mucosal damage. Therefore, improving the efficacy of intestinal mucosal perfusion therapies is key to protecting the intestinal barrier function.

In critically ill patients, another feature associated with intestinal barrier dysfunction is uncontrolled intestinal bacterial overgrowth which can be treated by antimicrobial drugs such as neomycin, gentamicin, metronidazole or by application of mechanical cleaning methods to remove bacteria which results in a reduction in bacterial translocation. These methods are still recommended in the clinic, although there have been no strict clinical control reports to date, and the benefits from these treatments remain inconsistent.

The nutritional status of the intestine can be affected by hunger, excess nutrients, weight loss of more than 10% of normal body weight, and these respective changes can alter intestinal morphology and function.

Nutrients within the intestinal lumen play an important role not only in

affecting the growth and function of intestinal epithelial cells, but also in stimulating the secretion of GI hormones that also promote intestinal cell growth. Therefore, in clinical situations where the GI function remains intact, early enteral nutritional interventions should be implemented in postoperative patients or critically ill patients after recovery. This can be carried out using a nasal feeding tube or *via* a jejunostomy tube when patients are incapable of orally taking in food. To promote cell growth and to regulate the intestinal immune function, arginine, glutamine, fish oil and nucleotides can be incorporated into food sources [12]. Animal experiments suggested that epidermal growth factor and insulin-like growth factors could stimulate protein synthesis and intestinal cell proliferation. It has now been confirmed that early enteral nutrition plays an important role in the maintenance of the normal mucosal structure and barrier function, preventing intestinal flora disorders, enhancing host resistance to infection and preventing hypermetabolism after surgery and trauma. Early enteral nutrition is an important countermeasure in the control of enterogenic infections.

Bifidobacteria comprise the dominant probiotic used in humans, can attach to the intestinal epithelium through teichoic acids, and can form a natural biological barrier with anaerobes such as *Lactobacilli. Bifidobacterium* and *Lactobacillus* produce acid as a metabolic by-product that lowers intestinal pH that negatively impacts the survival and proliferation of gram-negative bacteria and reduces the production and absorption of endotoxin (therefore reducing plasma endotoxin levels). In addition, oral administration of *Bifidobacteria* can increase IgA secretion, enhance non-specific phagocytosis and enhance local intestinal immunity. Furthermore, *Bifidobacteria* produce amino acids, cell proteins and vitamins that can be used by humans. Therefore, probiotic organisms like *Bifidobacteria* can play an important role in maintaining the ecological balance of the intestine, generating an environment that is not conducive to pathogen growth, protecting the intestinal mucosal barrier and improving the immune function [13]. It has been confirmed that oral administration of *Bifidobacterium* can be effective in preventing post-traumatic enterogenic infections.

19.5   Prevention and Prognosis of Surgical and Traumatic Infections

A combination of factors today has compounded the difficulties associated with treating surgery and trauma-related infections. Some of these compounding factors include a growing population of elderly patients, patients undergoing chemo- and radio-therapies, increased incidence of diabetes and cancer and a growing immune-suppressed population. These risk factors, combined with the weakened resistance of surgical patients following the use of anesthesia and surgical trauma, traumas caused by a variety of accidental injuries, the increased number of major surgeries and increased frequency of prosthetic surgical procedures, have significantly increased the chances for patients to develop intra-abdominal infections. Despite the use of multiple new antibiotics and novel treatment

methods, sepsis and other complications caused by traumatic infections are still difficult to prevent and treat. In the United States, severe wound infections leading to sepsis and shock (especially multiple organ failure) are the 10th leading cause of death in surgical patients. About 30% of surgical ICU patients suffer from sepsis leading to multiple organ dysfunction or failure that has become one of the major causes of death in surgical patients. It is clear from these observations that surgeons need to focus on establishing novel prevention strategies designed to curb the frequency of surgery and trauma-related infections.

19.5.1   *Prevention of Post-Surgical and Post-Traumatic Infections*

We will introduce the following measures to prevent post-surgical and post-traumatic infections in this section.

19.5.1.1   Improvement of Pre-Surgery Prophylaxis

It has been proven that strengthening preoperative treatments can significantly reduce the incidence of surgery and trauma-related infections. Awareness of surgical asepsis must be emphasized and operating room management must be strengthened [14]. In particular, emergency surgeries, preoperative hospital stays, operation times and the patient's health must be considered in the context of bacterial infections. The risk of surgical site infections can be significantly reduced if the following risk factors are addressed [15].

Maintaining normal temperature. Independent of the use of general, spinal or epidural anesthesia, patient body temperature can decrease by 1 – 3 ℃, resulting in significant reductions in the immune function and reduced surgical site blood flow, resulting in an increased risk of SSIs. Therefore, the use of thermal equipment and measures to maintain body temperatures at or above 36 ℃ during surgical procedures is recommended.

Optimizing oxygen tension. Post surgical administration of 80% oxygen has been shown to reduce post-surgical wound infections and postoperative nausea and vomiting rates [16]. Therefore, it is recommended that intubated surgical patients receive 80% oxygen (>12 L/min) *via* inhalation using a non full-face breathing mask for up to 2 hours post surgery.

Blood glucose control. Maintaining blood glucose levels at a stable level is especially important for patients undergoing coronary artery bypass graft surgery. Furthermore, control of pre-surgical blood sugar levels is particularly critical since elevated blood glucose increases the risk of postoperative infections (POI). Hyperglycemia has been linked to leukocyte function abnormalities, including granulocyte adherence, impaired phagocytosis and delayed chemotaxis. These leukocyte deficiencies are associated with increased infections and infection risks have been shown to be reduced if glycemic control is maintained. Using a closed-looped artificial pancreas system to maintain constant glycemic levels

without increasing the risk of hypoglycemia might be a safe and useful blood glucose control system in critically ill surgical patients [17]. At present, however, the preoperative optimal target range for blood glucose to reduce POI remains undefined.

Depilation of the surgical site. Traditional shaving one day prior to surgery has proven ineffective in preventing infections and in some cases promotes colonization of the shaved sited since some microorganisms colonize shaving-associated micro abrasions. Surgical areas that have limited amounts of hair do not necessitate shaving and areas with more hair can be shaved using clippers or an electric razor and this can be carried out immediately before surgery in the operating room (particularly if razors are to be used, *e.g.*, craniotomy).

Surgical environment. It is important to strictly abide by the principles of aseptic surgery. Infections of the incision site are related to loss of live tissues, residual foreign bodies, blood clots or dead space. To date, wound irrigation with antibiotic-containing solutions is not common practice.

Hospital stay. A simple, cost-effective means of reducing infections is to remove patients from hospital environments as quickly as possible so as to remove them from an environment containing an array of pathogens capable of infecting the surgical site.

19.5.1.2   Prophylactic Antibiotic Therapies

Antimicrobial prophylaxis for the preventions of SSI is one of the most widely accepted and used surgical practices. Effective prophylaxis requires adhering to safe surgical practices in combination with the appropriate antimicrobials administered in correct dosages for finite periods of time.

There is no question that antibiotics serve as an effective prophylactic strategy for the prevention of SSI but they are not needed for all operations. Generally, Class I incisions (clean incisions) are carried out under strict aseptic conditions and should not require prophylactic antibiotic use. Prophylactic antibiotics are used for Class II incisions (clean incision) and the less contaminated Class III incisions. Most serious contamination is associated with Class III and IV type incisions. These include open wounds and gastrointestinal perforations that should be treated with antibiotics before and after surgery.

Specific indications of prophylactic antibiotic use. (i) Class II incision cleaning involves wounds with contamination at the wound site, typically involving surgery of the GI tract, oropharynx, respiratory tract and the female reproductive tract. (ii) The use of artificial materials or manually operated devices, such as artificial heart valve replacement surgery, artificial vascular grafts or artificial joint replacement surgery. (iii) Major surgery or surgery lasting for many hours, trauma patients or in the case of infections, serious, consequences such as craniotomy and heart surgery, establishing portosystemic shunts or carrying out splenectomies. (iv) Patients with risk factors for infection, such as old age, diabetes, immune dysfunction or malnutrition.

Parameters associated with prophylactic antibiotic usage. (i) The first dose

should be administered before incision. The timing of administration is critical and should start 20 – 30 min before surgery (during induction of anesthesia) to ensure delivery prior to any potential contamination and so that appropriate antibiotic tissue concentrations are reached (MIC > 90). Antibiotics should be administered in the operating room. In order to avoid infusion reactions, fluoroquinolones and vancomycin should be administered 2 h before surgery. The use of vancomycin as a prophylactic is limited to use when there exists a potential risk of MRSA infections. Post surgery antibiotic treatments should be stopped within 24 h since it has been demonstrated that extending prophylactic antibiotic usage past this time does not diminish infection risks. (ii) The entire dosage of prescribed antibiotics should be administered for maximum efficacy. The upper range of the dose should be considered for larger patients or those undergoing longer operations. Specifically, antibiotic dosing should be based on a patient's weight or body surface area. Cephalosporins that have a serum half-life of 1 – 2 h are commonly used to ensure that effective drug concentrations are maintained during the entire surgical procedure, particularly if the operation exceeds 3 – 4 h. In these cases, up to three dosages may need to be administered. Antibiotics should be administered intravenously and administration completed within 20 – 30 min. Delivery should take place drop-wise and slowly to achieve effective concentrations. (iii) Re-dosing should be considered for longer surgery, for example, patients undergoing surgery that extends beyond two antibiotic half-lives should be re-dosed during surgery. Generally, the antibiotics selected for this process should be of short-range use and should not be used during elective surgeries. If the patient presents significant risk factors for infection, particularly during surgery involving prosthesis or implants, antibiotic use can be extended for several days or even until the stitches are removed to reduce the risk of developing SSIs. (iv) Choosing an appropriate antibiotic is also critical to ensuring success. Antibiotics should be chosen on the basis of their effectiveness against pathogens most likely to be encountered during the course of a particular surgery rather than selecting broad-spectrum antibiotics. Common microbial targets considered during antibiotic selection include microbes comprising the normal skin flora (*e.g.* staphylococci). In these cases, first-generation cephalosporins are frequently selected. Although intravenous administration is the most common route, combinations of oral and intravenous routes can also be used. If anaerobic infections are expected, metronidazole and other anti-anaerobic-selective drugs can be used. From an economic, safety and antibiotic-resistance perspective, it is recommended that relatively narrow-spectrum antibiotics be selected and to avoid the use of new, broad-spectrum antimicrobial agents. The preventive treatments for fungal infections remain controversial.

19.5.2   Conventional Treatments Associated with Surgery and Wound Infections

Conventional treatments associated with surgery and wound infections include

antibiotic therapies controlling the infection source.

19.5.2.1   Antibiotic Therapies

At present, treatment of surgical and traumatic infections primarily employs the use of antibiotics. However, antibiotics are not capable of effectively controlling some infectious agents due to the development of widespread drug-resistance. This problem should prompt us to modify our use of antibiotics to minimize the emergence of resistant strains by first determining the antibiotic resistance profile of respective clinical isolates. This will allow for the selection of the most effective antibiotic for the treatment of specific infections.

A better understanding of how antibiotics function (including their mechanism of action and its impact on microorganisms and the human body) will also help to select the most effective antibiotics for the treatment of different infections. This knowledge is important since some antibiotics increase bacterial toxin production (*e.g.* lipopolysaccharide and peptidoglycan). The release of antibiotic-induced endotoxin is both dose- and drug-dependent. Experiments measuring *E. coli* endotoxin release in the presence of antibiotics at doses 50-fold, the MIC showed that endotoxin release was unchanged in the presence of meropenem or imine, but differences were observed in the presence of ceftazidime. Selecting antibiotics that confer their antimicrobial effects *via* different mechanisms may circumvent the problems observed with antibiotics that increase toxin production, *e.g.* rifampicin led to minimal release of lipoproteins and teichoic acids; half as much as were released in the presence of dalfopristin and a quarter of the amount released in the presence of ceftriaxone. Clinically, we want not only to clear the pathogen but also to minimize toxin production associated with antibiotic usage. This will require experiments that define toxin-production profiles for different antibiotics.

When patients are being treated with antibiotics post-surgery, it is important to pay close attention to the clinical response. If infections develop, the original treatment strategy should be modified to include an increased dose or frequency of administration, consider combination therapies to widen the antibacterial spectrum, carefully select the antimicrobial drugs used and consider anti-fungal treatments when fungal infections are suspected. In addition, surgical interventions (including drainage and debridement) should be considered while actively searching for the focus of infection. Once the patient's vital signs stabilize, that is, infection symptoms and signs have disappeared, body temperature and white blood cell counts reach normal levels for 3 d, antibiotic treatment can be stopped.

19.5.2.2   Controlling the Infection Source

Dealing with the source of infection is important in the treatment of surgical and wound infections. Treatments include abscess drainage, removal of necrotic tissues and potentially infected devices and controlling/limiting bacterial contamination. Once a focus of infection is identified, it should be dealt with

promptly. Draining abscesses encased in a cellulose capsule will help drain necrotic tissues. If located percutaneously, abscess drainage can be carried out under the guidance of ultrasound or CT which significantly increases the success rate.

Debridement is the process of removing necrotic, solid tissues while leaving healthy tissues intact as a means of facilitating the healing process. Identifying healthy tissues, however, can sometimes be challenging, especially under conditions of low perfusion or bowel necrosis caused by thrombus. These complications in the gut make it difficult to determine the scope of bowel resection required. Regarding necrotic tissue surrounding the pancreas, it is important to delay necrotic tissue removal and debridement should be conducted at multiple times since necrosis develops in stages in this tissue. In addition, avoiding uncontrolled bleeding is facilitated following CT examination that can be used to assess tissue health before and after surgery.

In the context of heart surgery, clinicians should give priority to the removal and replacement of vascular access devices after it has been established that other indwelling devices are not the source of infection. Treatments are more difficult when left ventricle assisting devices are in place and patients have artificial heart valves. Mortality rates are high from these types of postoperative complications.

Once the infection foci are identified, selecting the most effective removal strategy is the key to minimizing post-operative morbidity and mortality. In general, measures used to control the infection source ought to minimize damage to the body so that patients can recover more rapidly. Removal of foci should be rapid and, if possible, cause little or no damage to the patient. Patients suffering from necrotic cholecystitis or secondary sepsis should be treated by percutaneous cholecystostomy under radiation. Percutaneous drainage is superior to surgical drainage for intra-abdominal abscesses presenting formed capsules. Utilizing minimally invasive surgical procedures such as laparoscopy should be considered in cases of severe surgical infection. The advantage of laparoscopy is that it has few complications and patients have a quick recovery time even in cases of complicated intra-abdominal abscesses, bile peritonitis or delayed hemoperitoneum. The choice of the surgical procedure selected and when the procedure is carried out must be determined in the context of the patient's health. If the patient's condition does not improve, the treatment approach will have to be modified. Failure to control the source of infection will result in a series of complications that include nutritional and metabolic imbalances accompanied, potentially, by multiple organ failure.

19.5.3   Complications of Severe Surgical and Wound Infections Prevention and Treatment of Sepsis and MOF

Sepsis and MOF are serious complications associated with surgery and trauma. Their treatment, in addition to the above-mentioned conventional methods, requires intensive care and adoption of early goal directed therapy (EGDT) during

the early stages of sepsis or shock. Patients suspected of sepsis/shock should receive anti-shock therapy, timely glucocorticoid treatment, have blood glucose levels stabilized and treated with anticoagulants in order to prevent MOF when septic shock occurs. It is also important to provide effective nutritional support, particularly in septic patients also affected by malnutrition due to the energy consumed by the high metabolic processes associated with immune function decline (resulting from hyper-stimulation and the resulting cytokine storm) resulting in a sub-clinical MOF state. Treatment measures must be carried out according to the organs affected during the course of MOF, since the mortality rates of septic patients with acute renal dysfunction was significantly higher and about 60% required renal replacement therapy.

It is still undetermined if it is beneficial to reduce inflammatory mediators *via* continuous renal replacement therapy (CRRT), but some studies have shown that early and continuous veno-venous hemodiafiltration (CVVHDF) can improve the prognosis of patients with sepsis and organ failure. In addition, the efficacy of specific antibodies and antagonists used to limit immune dysfunction during the course of MOF remains inconclusive. The application of Chinese medicine also needs to be further studied in the context of MOF.

The goal-directed therapy commonly used in ICU refers to a titration-style treatment under the guidance of dynamic and quantitative targets while at the same time broadening the treatment according to different levels of monitoring indicators and combined with appropriate therapeutic tools needed to complete the treatment.

If the goal-directed therapy specifically targets disease at a certain stage, the timing of the therapy becomes critical to success, for example EGDT that targets severe infections and septic shock. At the early stage of sepsis and septic shock, appropriate treatment strategies used to treat or prevent local or systemic hypoperfusion and hypoxemia resulting from infections, hypotension, mental confusion, oliguria, lactic acid build-up, decreased oxygen levels in the superior vena cava, can all lead to an improved health status.

One study demonstrated that using EGDT, combined with blood transfusions and vasoactive and inotropic drug therapies to improve myocardial contractility of septic patients, enhanced tissue perfusion and reduced hypoxemia. These results showed that EGDT significantly reduced the incidence of both MOF and mortality. Reuben *et al*. recommended that patients that developed severe sepsis and septic shock should receive EGDT as soon as possible. EGDT administration, however, requires that clinicians act in a timely manner and accurately diagnose the patient's condition.

At present, it is believed   that nutritional support provided to septic and MOF patients serves to maintain the structure and function of tissues and organs and the improved metabolism reduces deterioration of the intestines and promotes healing, resulting in improved survival rates in septic patients. However, nutritional support should be administered only at appropriate time. A patient's electrolyte imbalance during the early stages of shock must first be normalized prior to the administration of nutritional support.

Typically, nutritional support is implemented when respiratory, circulatory

function, liver and kidney functions are stable and blood sugar levels are under control. Nutritional support is administered to septic patients parenterally (parenteral nutrition, PN) and/or enterally (enteral nutrition, EN). The advantages of these methods are that they reduce complications associated with single-use and the cost of the treatment. At the same time, PN can supplement nutrients that cannot be delivered by EN. It is important in the context of disease prevention that the structure and function of the small intestine should be maintained in septic patients. PN is conducive to maintaining intestinal integrity and function and in stabilizing the growth of normal intestinal flora, while at the same time reducing endotoxin release and bacterial translocation. PN should be administered as long as the patient's intestinal anatomy and function remain intact. PN can be first administered when sepsis patients with different degrees of intestinal dysfunction cannot receive EN. As the disease stabilizes, both PN and EN can be administered prior to transitioning to EN or oral diets. The main principles of gastrointestinal dysfunction treatment in the context of MODS are to prevent occult shock, improve GI ischemia, restore the intestinal architecture and GI motility. Once GI function is restored, early enteral nutrition can be started. In addition, EN will effectively stimulate the gastrointestinal mucosal barrier, reduce inflammation and prevent gut-pathogen associated sepsis. In addition, EN has been shown to improve the immune function.

Nutritional support is a part of comprehensive sepsis treatments. In order to stabilize patients, rational nutritional support combined with effective control of the infection should be considered.

Use of traditional Chinese medicines to treat sepsis has a long history and this field has uncovered new information relating to novel treatment strategies. Domestic scholars have verified using animal models and clinical studies show that rhubarb and other Chinese medicines possess therapeutic properties capable of restoring GI motility, protect the GI mucosa and prevent microecological disturbances. At present, traditional Chinese medicine used for experimental and clinical treatment of MODS can also be used to treat other maladies. Traditional Chinese medicine treatment modalities can be divided into either detoxification, Huayu, Tongfu or Fuzheng. The main medicinal components used for detoxification and Huayu are reduqing (honeysuckle, dandelion, Daqingye, heartleaf houttuynia herb), 912 (astragalus, Chinese angelica, red peony, Danshen) and Xuebijing (safflower, red peony, Chuanxiong, Danshen, Chinese angelica). The main medicinal components used for Tongfu are Cudong particles (rhubarb, Magnolia officinalis). The Shuangqing particles (Bupleurum root, astragalus, gypsum, Zhimu) not only have a role in detoxification and Huayu, but also in Fuzhengyangyin and Qixueliaqing. The above-mentioned traditional Chinese medicines have been proved effective in animal studies and small-scale clinical applications.

At present, it is imperative for these drugs to be tested in prospective studies carried out at multiple sites as a means of enrolling significant numbers of patients to study the effects of these treatments on sepsis and MODS and then based on these data, develop integrated programs combining Chinese and Western medicines to improve the prevention and treatment of sepsis and MOF.

19.5.4   *Future Directions*

In recent years, a reduction in the number of novel antibiotics available for the treatment of gram-negative and gram-positive bacterial infections (in addition to fungal infections) due to the rise in drug-resistant organisms has resulted in significant challenges in treating pre- and post-surgical/trauma-related infections. Novel antimicrobial peptides (as an alternative to antibiotics) have been identified from a variety of organisms (including bacteria, fungi, plants, insects, amphibians, fish, birds, mammals and humans) that represent a potentially new method of treating bacterial infections in the future. In addition, new treatment methods are constantly evolving. For example, one study found that a number of factors that contribute to cellular apoptosis (including lymphocyte-, neutrophil-, dendritic cell- and GI epithelial cell-related factors) have an important role in controlling the progression of sepsis, shock and MODS. Results in mice demonstrated that animals fed oral protease inhibitors not only presented a decrease in apoptosis of lymphocytes, but also presented an increase in sepsis survival rates, suggesting that inhibiting apoptosis in lymphocytes may represent a new strategy for the treatment of sepsis. We believe that problems relating to surgery and trauma-related infections will be solved by a combination of therapies resulting from the discovery of novel treatment modalities.

References

[1] Fry D E. A systems approach to the prevention of surgical infections. Surg Clin North Am, 2009, 89: 521-537.

[2] Kamp-Hopmans T E, Blok H E, Troelstra A, *et al*. Surveillance for Hospital-acquired infections on surgical wards in a Dutch university hospital. Infect Control Hosp Epidemiol, 2003, 24: 584-590.

[3] Martin L W, Altemier W A, Reyes P M Jr. Infections in pediatric surgery. Pediatr Clin North Am, 1996, 16: 735-766.

[4] Lee J A, Kim M S, Kim D H, *et al*. Postoperative infection and survival in osteosarcoma patients. Ann Surg Oncol, 2009, 16: 147-151.

[5] Gross T, Kaim A H, Regazzoni P, *et al*. Current concepts in posttraumatic osteomyelitis: A diagnostic challenge with new imaging options. J Trauma, 2002, 52: 1210-1219.

[6] Steven M, Gordon, M D. Antibiotic prophylaxis against postoperative wound infections. Clevel and Clinic Journal of Medicine, 2006, 73: 42-45.

[7] Lee CK, Hansen SL. Management of acute wounds. Clin Plast Surg, 2007, 34: 685-696.

[8] Sarkar B, Napolitano LM. Necrotizing soft tissue infections. Minerva Chir, 2010, 65: 347-362.

[9] Rea W J, Wyrick W J Jr. Necrotizing fasciitis. Ann Surg, 1970, 172: 957-964.

[10] Hang C H, Shi J X, Li J S, *et al*. Alterations of intestinal mucosa structure and

barrier function following traumatic brain injury in rats. World J Gastroenterol, 2003, 9: 2776-2781.

[11] Shen T Y, Qin H L, Gao Z G, *et al*. Influences of enteral nutrition combined with probiotics on gut microflora and barrier function of rats with abdominal infection. World J Gastroenterol, 2006, 12: 4352-4358.

[12] Quan Z F, Yang C, Li N, *et al.* Effect of glutamine on change in early postoperative intestinal permeability and its relation to systemic inflammatory response. World J Gastroenterol, 2004, 10: 1992-1994.

[13] Xia Y, Yang Z, Chen H Q, *et al.* Effect of bowel preparation with probiotics on intestinal barrier after surgery for colorectal cancer. Zhonghua Wei Chang Wai Ke Za Zhi, 2010, 13: 528-531.

[14] Daniel I, Sessler M D. Non-pharmacologic prevention of surgical wound infection. Anesthesiol Clin, 2006, 24: 279-297.

[15] Mangram A J, Horan T C, Pearson M L, *et al*. Guideline for prevention of surgical site infection. Infect Control Hosp Epidemiol, 1999, 20: 250-278.

[16] Belda F J, Aguilera L, García de la Asunción J, *et al*. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. JAMA, 2005, 294: 2035-2042.

[17] Hanazaki K, Maeda H, Okabayashi T. Relationship between perioperative glycemic control and postoperative infections. World J Gastroenterol, 2009, 15: 4122-4125.