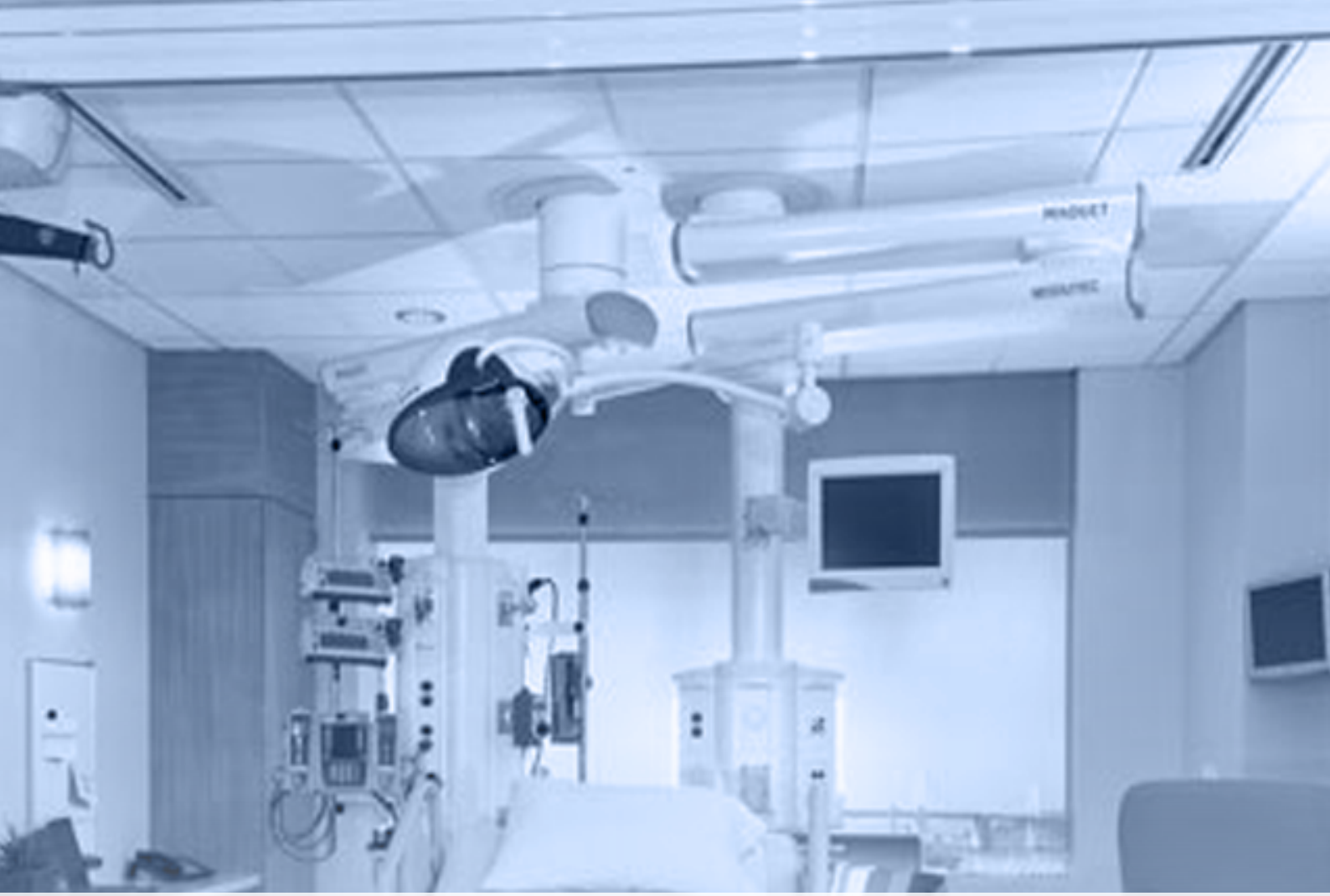

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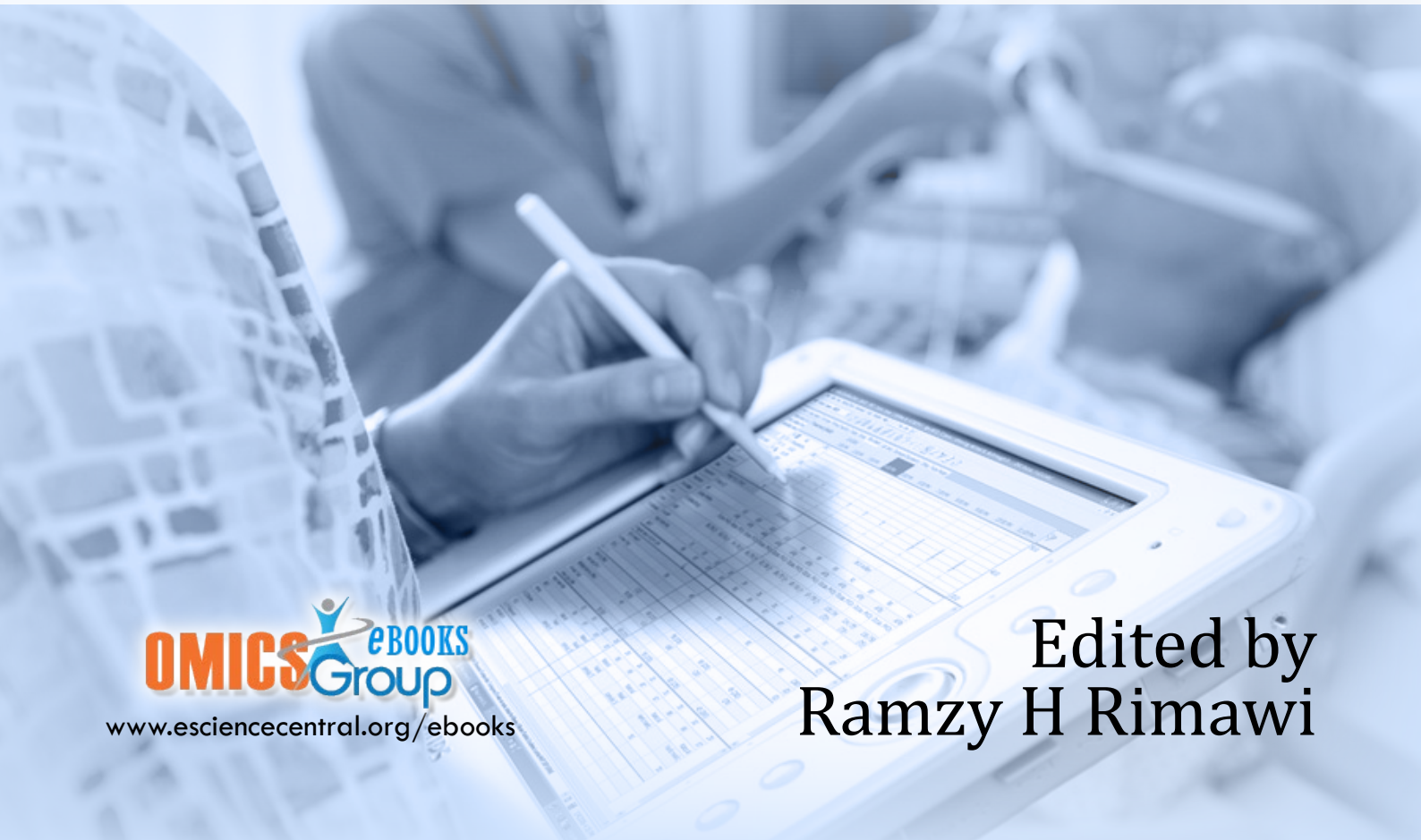

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Antibiotic Therapy in Sepsis

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Abstract

Sepsis is a major cause of morbidity and mortality in the intensive care unit (ICU). While source control is the number priority in the management of the septic patient, antibiotic therapy is a cornerstone in the management of patients with sepsis. Empiric broad spectrum antibiotics are recommended within 1 hour of suspected sepsis, as every hour delay is associated with a 6% rise in mortality. In addition, many septic patients require intravenous fluid resuscitation, vasopressors, mechanical ventilation and hemodialysis to support organ function. While recommendations for appropriate antibiotic expenditure are often being updated, we will discuss the empiric antibiotics that should be initiated for major infections treated in the ICU.

Keywords: Sepsis; Septic shock; Antibiotics; Critical care; Infections

Introduction

The evaluation and management of sepsis is an everyday concern in the intensive care unit (ICU) setting. The sepsis syndrome is, in part, caused by an amalgamation of host response to pathogens. Broad spectrum antibiotics are recommended within 1 hour of suspected sepsis, as every hour delay is associated with a 6% rise in mortality [1,2]. Regardless of the infection site, daily measures to tailor antibiotic therapy should be done in order to avoid potential adverse effects, resistance and increased healthcare costs. In this chapter, we will discuss the major infections encountered in the ICU and recommended empiric antibiotic therapies. In the US, common infections in the medical ICU include pneumonia (30%), urinary tract infection (30%), bloodstream infections (16%), cardiovascular infections (5%), gastrointestinal infections (5%), ear/nose/throat infections (4%), and skin/soft-tissue infections (3%) [3].

Sepsis Criteria

Sepsis is the presence the systemic inflammation with a suspected or documented infection. Signs of systemic inflammation include [1]:

- Hyperthermia or hypothermia
- Tachycardia
- Tachypnea
- Altered mentation
- Leukocytosis or leucopenia
- Plasma C-reactive protein more than two SD above the normal value
- Elevated Plasma procalcitonin

Severe Sepsis is organ dysfunction as a result of an underlying infection, including hypoxemia, oliguria, azotemia, coagulopathy, thrombocytopenia, hyper bilirubinemia, and abnormal tissue perfusion markers (e.g., hyperlactatemia and decreased capillary refill) [4]. Septic shock suggests concomitant hemodynamic instability (systolic blood pressure <90 mmHg, mean arterial pressure <70 mmHg or a decrease in systolic blood pressure by >40 mmHg or less than two SD below normal for age) despite aggressive fluid resuscitation.

Antibiotic Therapy

Immediate initiation of empiric antibiotic therapy is strongly recommended when the likelihood of infection is high in the setting of progressive organ dysfunction. Several studies have demonstrated a reduction in morbidity and mortality when appropriate initial antibiotics are chosen [5-8]. However, antibiotics should not be used in patients with noninfectious causes of severe inflammatory response syndromes. The use of appropriate cultures and biomarkers (e.g., procalcitonin) may be used to help discontinue empiric antibiotics within 3-5 days in patients who have systemic inflammation, but eventually determined not secondary to an infectious cause. Furthermore, similar attention should be given to timely cessation of antibiotic therapy after an appropriate course,. The Surviving Sepsis Campaign recommends duration of therapy of 7 to 10 days when clinically indicated in patients without slow clinical

response, undrainable foci of infection, bacteremia with *S. aureus*; some fungal and viral infections, or immunologic deficiencies, including neutropenia [1].

Selection of appropriate antibiotic therapy in the ICU is based on several factors. Institutional or regional antibiograms should be taken into consideration whenever selecting an appropriate antibiotic therapy. Bioavailability and tissue penetration of variable antibiotics in particular sites, including lungs, central nervous system, bone, must also be taken into consideration. Drug clearance is another matter, as many antibiotics are cleared renally (exceptions include macrolides, clindamycin, tetracyclines, linezolid, ceftriaxone, anti-staphylococcal penicillins, voriconazole, amphotericin B and caspofungin) or hepatically. Toxicity profile, including hematologic or hepatic effects,must be considered. Many intravenous antibiotics require co-administration with intravenous fluids; this may become important in patients on fluid restriction. Although cost represents a lesser concern during decision making in infectious disease management, it is, nonetheless, of great importance and relevant financial issues should be considered.

Pneumonias in the ICU

Pneumonia is the second most common cause of hospital-acquired infection in the ICU, mostly occurring in mechanically ventilated patients [9,10]. Although the discussion of pneumonia in the ICU is further discussed in another chapter, we will briefly discuss the recommended empiric antibiotic therapy in community-acquired pneumonia (CAP) and healthcare-associated pneumonia (HCAP).

Community-acquired pneumonia is defined as a constellation of suggestive clinical features and a demonstrable infiltrate by chest radiograph in a patient outside of hospital or extended living facilities. Recommended empiric therapy for patients admitted to the ICU with CAP includes [11]:

- Beta-lactam (ceftriaxone, or ampicillin-sulbactam) plus azithromycin
- If penicillin-allergic, a fluoroquinolone and aztreonam are recommended
- If *Pseudomonas* infection is suspected, an antipneumococcal, antipseudomonal b-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus a fluoroqinolone (ciprofloxacin or levofloxacin 750-mg dose) or an aminoglycoside and azithromycin
- If community-acquired methicillin-resistant *Staphylococcus aureus* is suspected, add vancomycin or linezolid.
- If influenza is suspected, antiviral therapy (i.e., oseltamivir) should be added.

Healthcare-associated pneumonia is defined as an evident radiographic infiltrate with suggestive clinical features in a patient with the following risk factors: antimicrobial therapy or hospitalization ≥2 days in the preceding 90 days, current hospitalization of ≥5 days, high frequency of antibiotic resistance in the community or hospital unit, residence in a nursing home or extended care facility, home infusion therapy (including antibiotics), chronic dialysis within 30 days, home wound care, family member with multidrug-resistant pathogen, immunosuppressive disease and/or therapy [12]. HCAP is included in the spectrum of hospital-associated and ventilator-associated pneumonias. For uncomplicated HCAP in patients with good clinical response, 7-8 days is the recommended duration if the infection does not involve *Pseudomonas* aeruginosa or Acinetobacter. Combination empiric therapy for a specific pathogen should be aimed at multi-drug resistant pathogens (Table 1). Often, double-gram negative coverage is given in case a multi-drug resistant *Pseudomonas* may be resistant to one of the agents given. If possible, therapy should be de-escalated to just one agent when in-vitro susceptibility data is acquired.

Potential Pathogen	Recommended Antibiotics
Streptococcuspneumoniae *Haemophilus influenza* *Escherichia coli* *Proteus* spp. *Enterobacter* spp. *Serratia* spp. *Klebsiella* (non-carbapenemase producing)	Ceftriaxone or Fluoroquinolone or Ampicillin-sulbactam or Ertapenem
Methicillin-sensitive *S. aureus*	Penicillinase-penicillin (e.g., Nafcillin) or Cephalosporin
Methicilllin-resistnat *S. aureus*	Vancomycin or Linezolid
Pseudomonas aeruginosa *Extended-spectrum beta-lactamase (ESBL) Klebsiellapneumoniae* *Acinetobacter spp.*	Cefepime, ceftazidime, imipenem, meropenem, doripenem, piperacillin-tazobactam + ciprofloxacin/levofloxacin or aminoglycoside (gentamicin, tobramycin, amikacin)

Table 1: Empiric antibiotic therapy for healthcare-associated pneumonias.

Urinary Tract Infections in the ICU

The National Nosocomial Infections Surveillance System in ICU patients reports that urinary tract infections (UTI) are the most common infections in critically ill patients and result in excess deaths, increased length of stay, and higher healthcare costs [3,13]. Complicated UTI arise when there is interference with normal voiding, which results in impaired flushing of bacteria from the genitourinary tract. Anomalies include pyelonephritis, indwelling catheter infections, nephrolithiasis, prostatic hypertrophy or obstruction, and spinal cord injuries or other neurologic deficits affecting the genitourinary tract. Admission to the intensive care unit alone is not an inclusion criteria for complicated UTI. The incidence of bacteruria in patients with indwelling catheters is 3-10%, with a substantial proportion of them (estimated 10-25%) developing UTI [14]. Although UTI's warrant antibiotic therapy, healthcare providers often treat urine culture results in the absence of genitourinary symptoms and in the presence of infections in other sites [15]. However, practitioners should be more circumspect before prescribing antibiotics in this circumstance.

A true catheter-associated UTI is defined as the presence of bacteruria with clinical symptoms including new onset or worsening of fever, rigors, altered mental status, malaise, or lethargy with no other identified cause; flank pain; costovertebral angle tenderness; acute

hematuria; pelvic discomfort; and in those whose catheters have been removed, dysuria, urgent or frequent urination, or suprapubic pain ortenderness [16]. The recommended duration of therapy is 7 days in patients who have prompt resolution of symptoms and 10-14 days in patients who have a delayed response. After the indwelling catheter is removed, a 3-day course may be considered in women ≤65 years old without evidence of pyelonephritis.

The most effective way to reduce the incidence of bacteruria is to reduce the use of urinary catheterization. This is done viacatheter restriction only to patients who have clear indications andremoval as soon as it is no longer needed. Several prospective, randomized trials of asymptomatic bacteriuria therapy consistently conclude that antimicrobial therapy for asymptomatic bacteriuria is not beneficial in most populations. In symptomatic patients, data on local antibiograms and antimicrobial resistance should be used to help guide empirical treatment. Although clinical trials of complicated UTI therapy have reported high efficacy rates for a wide variety of antimicrobial agents (including fluoroquinolones, piperacillin-tazobactam, carbapenems, aminoglycosides, and cephalosporins), there are limited comparative studies.

Unknown Source of Infection

Many times, when patients are initially admitted to the ICU, the causative etiology is unknown. Nevertheless, appropriate empiric antimicrobial selection should be rapidly initiated [17]. Most studies recommend starting with broad-spectrum combination therapy and de-escalating as per culture results. Biomarkers such as procalcitonin, can be used to further assist in decision whether to discontinue antimicrobial therapy [18]. Attempts should be made to obtain microbial cultures prior to initiation of antimicrobial therapy, as the argument can be made that the cultures are negative due to the antimicrobial suppression.

ICU Catheter-Related Bloodstream Infections

Admission into the ICU does not affect the management of catheter-related bloodstream infections (CRBSI). Central venous, arterial and dialysis catheters are commonly placed in the ICU, sometimes during urgent critical situations when sterility may be jeopardized. Therefore, intensive care units are a common setting for CRBSI, accounting for about 80,000 CRBSI's each year [19]. For patients who are hospitalized in the ICU with a new onset of fever but without severe sepsis or evidence of bloodstream infection, it is recommended to obtain simultaneous blood cultures from the non-tunneled central venous catheter, the arterial catheter (if present), and percutaneously, instead of performing routine catheter removal [20].

Vancomycin is recommended for empiric therapy in areas with elevated prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA). Daptomycin is a suitable alternative for suspected MRSA-CRBSI. Empiric therapy with an anti-*Pseudomonas* agent should be based on local antimicrobial susceptibility data, disease severity, existence of a femoral catheter in critically ill patients, and presence of neutropenia or known colonization with multi-drug resistant organisms. Empiric therapy for candidemia should be considered in patients with history of bowel surgery, prolonged broad-spectrum antibiotic use, solid-organ or bone marrow transplantation, femoral catherization, total parenteral nutrition, colonization with *Candida* at multiple sites, or hematologic malignancy.

Antibiotic therapy duration depends on the organism, whether the catheter was retained or removed, concomitant infections (e.g., infective endocarditis, osteomyelitis, abscess) and duration of bacteremia. For patients with persistent bacteremia/fungemia at least 72 hours after the catheter was removed, 4-6 weeks of therapy is recommended [20]. For coagulase-negative *S. aureus*, systemic antibiotic therapy should be given for 5-7 days if the catheter is removed, and 10-14 days with antibiotic lock therapy if the catheter is retained. For *Enterococcus* and gram-negative bacilli (e.g., *Pseudomonas*), 7-14 days of therapy is recommended after catheter removal. Catheter removal is strongly recommended in patients with candidemia, followed by 14 days of therapy after the first negative blood culture.

Gastrointestinal Infections in the ICU

Intra-abdominal infections are a major cause of morbidity, mortality and antibiotic expenditure in the ICU [21]. Accurate and timely diagnosis can have a major impact on clinical outcome, antimicrobial selection, healthcare cost and need for surgical intervention. Spontaneous bacterial peritonitis in the ICU is commonly seen in decompensated cirrhotic patients, likely due to the translocation of overgrowing enteric bacteria (usually gram negative organisms, although MRSA has been commonly described in ICU patients) across an anatomically intact gastrointestinal tract. Gastrointestinal wall perforation or ulceration can result in polymicrobial seeding into neighboring areas, resulting in signs of acute abdomen. Localized pain suggests the infection is walled-off in the area directly associated with the area of seeding, whereas diffuse pain suggests generalized peritonitis. Intra-abdominal abscesses, bowel perforation, cholecystitis, and ascending cholangitis are common ICU gastrointestinal infections.

While antibiotic therapy plays an important role in the management of intra-abdominal infections, fluid resuscitation, physiologic organ system support and surgical intervention are also key factors that dramatically affect morbidity and mortality. Bladder pressure monitoring may be done to detect abdominal compartment syndrome as a complication of extensive intraperitoneal/retroperitoneal inflammation and aggressive fluid resuscitation [22]. Antibiotic therapy should be directed towards the culture results, if known. Otherwise, broad-spectrum therapy against gram-negative organisms and anaerobes (e.g., carbapenems, piperacillin-tazobactam, fluoroquinolones + metronidazole, tigecycline, 3rd/4th generation cephalosporin + clindamycin or metronidazole) should be given for 4-7 days, assuming there is adequate source control [23]. Source control is attained by adequate drainage, monitored by clinical improvement, and radiographic improvement of the fluid collection.

With increasing antibiotic and antacid use in the ICU, *Clostridium difficile* infection (CDI) is commonly seen in critically ill patients. For patients with severe, complicated CDI, oral vancomycin (per rectum if ileus is present) with or without intravenously administered metronidazole is the treatment of choice [24]. The reason for considering combination therapy is to increase the likelihood of tissue penetration and allow for clinical response. If a patient is already clinically improving on oral or per-rectal vancomycin, the addition of metronidazole is not necessary. In patients with rising hyperlactatemia and leukocytosis ≥50,000 cells/μL, subtotal colectomy with rectal preservation should be considered.

ICU Skin & Soft-Tissue Infections

While the majority of skin and soft-tissue infections do not often require intensive care (e.g., impetigo, cutaneous abscess, cellulitis, erysipelas), many still do, including necrotizing associated soft-tissue infections (NASTI), toxic-shock syndrome, Stevens-Johnson syndrome, toxic-epidermal necrolysis and burns. Clinical or radiographic features may help to guide clinicians into suspecting NASTI, including failure to respond to initial antibiotic therapy, clinical signs such as systemic toxicity (e.g., renal failure, altered mentation), a wooden feel of the subcutaneous tissue extending beyond the apparent skin involvement, bullae, skin necrosis, ecchymosis, crepitus, and/or CT/MRI evidence of fascial plane edema. In addition to rapid assessment for surgical intervention, aerobic and anaerobic antimicrobial therapy is recommended until the patient has demonstrated clinical improvement (defervesce ≥72 hours) and no further operative procedures are needed [25]. Clindamycin is often given due to the in-vitro studies demonstrating toxin suppression and cytokine production modulation and observational studies showing superiority to beta-lactam antibiotics in children with invasive *Streptococcus pyogenes* infections [26].

Conclusion

Antimicrobial selection in the ICU continues to have a fundamental impact on patient outcome, hospital cost, antimicrobial resistance, and potential adverse reactions. Frequent communication with microbiology, pathology and surgery are key components in optimizing patient care. Daily collaboration with Infectious Disease specialists can help curtail unnecessary antibiotic expenditure [27]. Many infections are treated similarly, whether the patient is critically ill in the medical intensive care unit, or stable on the medical wards, including empiric therapy for meningitis, encephalitis, bacterial endocarditis, and prosthesis infections [28-30]. Clinicians are strongly advised to be familiar with the "Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America," as culture acquisition and diagnostic testing will affect antimicrobial selection, which ultimately effect clinical outcome [9]. While in most cases empiric antibiotic therapy should be initiated before or during culture acquisition of unstable or critically ill patients, antimicrobial selection should frequently be reconciled in order to avoid potential adverse events, reduce incidence of antimicrobial resistance, reduce healthcare costs and improve patient outcome.

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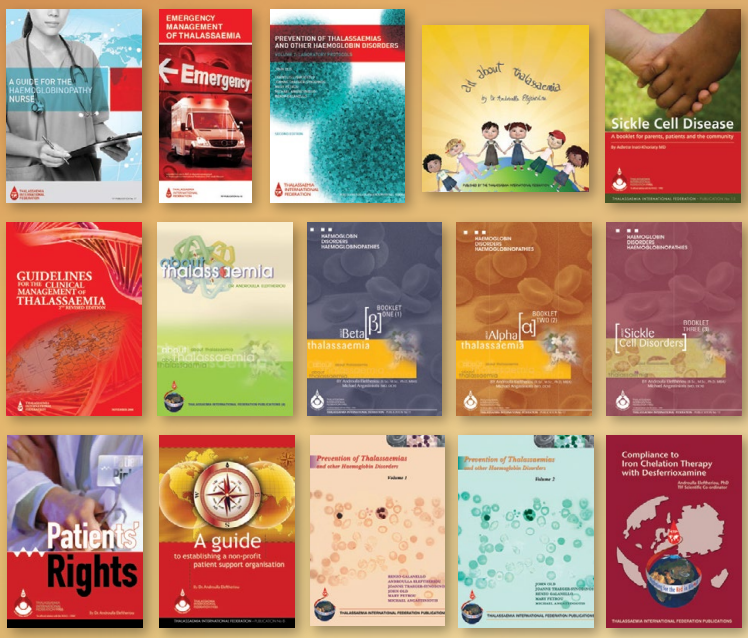

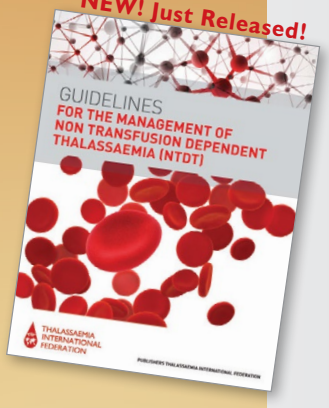

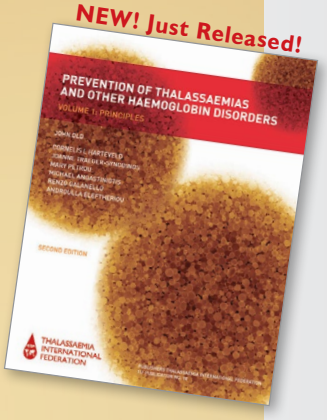

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