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<p>Sepsis guidelines and mandates encourage increasingly aggressive time-to-antibiotic targets for broad-spectrum antimicrobials for suspected sepsis and septic shock. This has caused considerable controversy due to weaknesses in the underlying evidence and fear that overly strict antibiotic deadlines may harm patients by perpetuating or escalating over-treatment. Indeed, a third or more of patients currently treated for sepsis and septic shock have noninfectious or nonbacterial conditions. These patients risk all the potential harms of antibiotics without their possible benefits. Updated Surviving Sepsis Campaign guidelines now emphasize the importance of tailoring antibiotics to each patient’s likelihood of infection, risk for drug-resistant pathogens, and severity-of-illness.</p>	
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<p>Both cytokine release syndrome (CRS) and sepsis are clinical syndromes rather than distinct diseases and share considerable overlap. It can often be challenging to distinguish between the two, but it is important given the availability of targeted treatment options. In addition, several other clinical syndromes overlap with CRS and sepsis, further making it difficult to differentiate them. This has particularly been highlighted in the recent coronavirus disease-2019 pandemic. As we start to understand the differences in the inflammatory markers and presentations in these syndromes, hopefully we will be able to enhance treatment and improve outcomes.</p>	
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<p>Future pandemics will certainly arise and continue to have a profound impact on health care, including management within the intensive care unit. Robust preparedness plans require specific attention to detail as it pertains to incident management, surge capacity, infection control practices, and the health care workforce. The COVID-19 pandemic highlighted many gaps in prior preparedness efforts, and those lessons learned must be integrated into updated preparedness work. Additionally, ensuring health care workforce wellness, decreasing health care disparities, strengthening networks for rapid research and response, and active roles</p>	

in dispelling misinformation within the media should be integrated into pandemic preparedness plans.

**Management of Severe and Critical COVID-19 Infection with Immunotherapies**

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Janhavi Athale, Jolie Gallagher, and Lindsay M. Busch

Following the reduction in mortality demonstrated by dexamethasone treatment in severe COVID-19, many targeted immunotherapies have been investigated. Thus far, inhibition of IL-6 and JAK pathways have the most robust data and have been granted Emergency Use Authorization for treatment of severe disease. However, it must be noted that critically ill patients comprised a relatively small proportion of most of the trials of COVID-19 therapeutics, despite bearing a disproportionate burden of morbidity and mortality. Furthermore, the rapidity and fluidity with which clinical trials have been conducted in the pandemic setting have contributed to difficulty in extrapolating available trial data to critically ill patients. The exclusion of many patients requiring invasive mechanical ventilation, preponderance of ordinal scale based endpoints, and frequent lack of blinding are particular challenges. More data is needed to identify beneficial treatments in the complex milieu of critical illness from COVID-19 infection.

**Supportive Care in Patients with Critical Coronavirus Disease 2019**

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Daniel A. Sweeney and Atul Malhotra

Specific therapies for the treatment of coronavirus disease 2019 (COVID-19) have limited efficacy in the event a patient worsens clinically and requires admission to the intensive care unit (ICU). Thus, providing quality supportive care is essential to the overall management of patients with critical COVID-19. Patients with respiratory failure not requiring intubation should be supported with noninvasive positive pressure ventilation, continuous positive airway pressure, or high flow oxygenation. Use of these respiratory modalities may prevent patients from subsequently requiring intubation. Basic components of supportive care for the critically ill should be applied equally to patients with COVID-19 in the ICU.

**Management of Highly Resistant Gram-Negative Infections in the Intensive Care Unit in the Era of Novel Antibiotics**

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Cornelius J. Clancy and M. Hong Nguyen

Antimicrobial-resistant bacterial infections, particularly those caused by Gram-negative bacteria, are major public health threats globally. Since 2015, several antibiotics with activity against highly antimicrobial-resistant Gram-negative bacteria have been approved, which offer alternatives to previous frontline agents such as polymyxins and aminoglycosides. Despite data that new drugs are more effective and better tolerated than older agents against at least some highly antimicrobial-resistant Gram-negative bacterial infections, clinicians remain uncertain about how best to incorporate them into clinical practice. In this article, we discuss the management of highly resistant Gram-negative bacterial infections in the era of new antibiotics, with particular attention to those caused by AmpC- and extended-spectrum  $\beta$ -lactamase-producing

Enterobacterales (which manifest phenotypically as 3rd generation cephalosporin resistance), carbapenem-resistant Enterobacterales, multidrug-resistant *Pseudomonas aeruginosa*, carbapenem-resistant acinetobacter baumannii, and *Stenotrophomonas maltophilia*.

**Management of Unique Pneumonias Seen in the Intensive Care Unit** 825

Brooke K. Decker, LaToya A. Forrester, and David K. Henderson

Infection of the lower respiratory tract is a potentially severe or life-threatening illness. Taking the right steps to recognize, identify, and treat pneumonia is critical to improving patient outcomes. An awareness of the diversity of potential infectious causes, the local endemic flora and resistance patterns, as well as testing strategies to differentiate causes of pneumonia is essential to providing the best patient outcomes. Understanding surveillance definitions allow intensivists to become partners in reducing hospital-associated infections and improving quality of care.

**Management of Common Postoperative Infections in the Surgical Intensive Care Unit** 839

Staci T. Aubry and Lena M. Napolitano

Postoperative infection and sepsis in the surgical intensive care unit (SICU) are common problems, and can be the reason for SICU admission or can be acquired during the SICU stay. Both diagnosis and management of infection and sepsis in the SICU can be complex, related to the surgical procedures performed, patient comorbidities, and resistant pathogens. The need for “source control” of postoperative infections can pose specific challenges and significant complexity in patient management. Postoperative infections in the SICU are associated with increased morbidity, mortality, and resource utilization, and therefore a strong focus on infection preventive strategies is warranted.

**ICU Management of Invasive  $\beta$ -Hemolytic Streptococcal Infections** 861

Ahmed Babiker and Sameer S. Kadri

$\beta$ -hemolytic streptococci (BHS) are a leading cause of invasive bacterial disease worldwide. They are subtyped based on the presence of the surface polysaccharide antigens and include Group A *Streptococcus* (GAS; *Streptococcus pyogenes*), Group B *Streptococcus* (GBS; *Streptococcus agalactiae*), and non-group A, non-group B *Streptococci* (NABS). Invasive BHS infection is defined as isolation from the normally sterile site in patients with a compatible clinical syndrome which include, but is not limited to, streptococcal toxic shock syndrome (STSS), Necrotizing soft tissue infection (NSTI), bacteremia, meningitis lower respiratory tract, musculoskeletal and puerperal/postpartum infections. Resuscitation, source control, and  $\beta$ -lactam therapy are the cornerstone of therapy.

**Severe *Clostridioides difficile* Infection in the Intensive Care Unit—Medical and Surgical Management**

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Ramzy Husam Rimawi, Stephanie Busby, and Wendy Ricketts Greene

*Clostridioides difficile* remains a major cause of morbidity and mortality in the intensive care unit, and therefore, *C difficile* guidelines are frequently being updated. Currently, fidaxomicin is the suggested treatment of initial and recurrent infection. Oral vancomycin is an acceptable alternative, followed by rifaximin and fecal microbiota transplantation. Bezlotoxumab is suggested in recurrent cases within 6 months. If patients fail to improve within 3 to 5 days of therapy, especially in patients who have had nasogastric tubes or emergent surgery, fulminant colitis is possible and surgical consultation should be considered for total colectomy.

**Uses of Procalcitonin as a Biomarker in Critical Care Medicine**

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Ryan C. Maves and Chukwunyelu H. Enwezor

Procalcitonin is a commonly used biomarker for infection and severity in the intensive care unit. Although relatively specific for bacterial, as opposed to viral, infections, serum procalcitonin levels also correlate with disease severity and thus cannot reliably distinguish between bacterial and nonbacterial infections in the setting of critical illness, particularly in cases of severe influenza and coronavirus disease-2019. Baseline procalcitonin levels are insufficiently discriminative to permit the withholding of antibiotics in patients with critical illness and suspected sepsis. Trends in procalcitonin levels over time, however, give us the opportunity to individualize the duration of antibiotics without negative impacts on mortality.