Rules of anti-infection therapy for sepsis and septic shock

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Abstract

Objective: Sepsis is a deadly infection that causes injury to tissues and organs. Infection and anti-infective treatment are the eternal themes of sepsis. The successful control of infection is a key factor of resuscitation for sepsis and septic shock. This review examines evidence for the treatment of sepsis. This evidence is combined with clinical experiments to reveal the rules and a standard flowchart of anti-infection therapy for sepsis.

Data Sources: We retrieved information from the PubMed database up to October 2018 using various search terms and their combinations, including sepsis, septic shock, infection, antibiotics, and anti-infection.

Study Selection: We included data from peer-reviewed journals printed in English on the relationships between infections and antibiotics.

Results: By combining the literature review and clinical experience, we propose a 6Rs rule for sepsis and septic shock management: right patients, right time, right target, right antibiotics, right dose, and right source control. This rule encompasses rational decisions regarding the timing of treatment, the identification of the correct pathogen, the selection of appropriate antibiotics, the formulation of a scientifically based antibiotic dosage regimen, and the adequate control of infectious foci.

Conclusions: This review highlights how to recognize and treat sepsis and septic shock and provides rules and a standard flowchart for anti-infection therapy for sepsis and septic shock for use in the clinical setting.

Keywords: Sepsis; Infection; Therapy

Introduction

Since the "Barcelona Declaration" was released by the European Society of Intensive Care Medicine (ESICM), the Society of Critical Care Medicine (SCCM), and the International Sepsis Forum (ISF) in 2002, the attempt to subdue sepsis has become one of the most important missions in critical care medicine worldwide. Some progress has been made in the past decade. The Surviving Sepsis Campaign (SSC) guidelines for sepsis management were published in 2004 and updated in 2008, 2012, and 2016.[1-4] The recently released 2018 online updates to the SSC guidelines first proposed the detailed procedure of 1 h bundles of resuscitation for septic shock. These guidelines have had a profound impact on the clinical practice of ICU doctors worldwide and over time have greatly improved the diagnosis and treatment of sepsis and septic shock.[5] However, the morbidity of sepsis continues to increase rapidly, and mortality has remained high (over 18%) in recent years.[6-10] The World Health Organization (WHO) has ranked conquering sepsis a top priority and urged global governments to invest greater efforts in this area during the 70th World Health Assembly in May 2017 [Figures 1 and 2].

The successful control of infection is a key factor of resuscitation for sepsis and septic shock. Based on years of clinical experience, we propose a 6Rs rule for sepsis and septic shock management: right patients, right time, right target, right antibiotics, right dose, and right source control. This 6Rs rule encompasses 6 core principles of anti-infection therapy for sepsis and septic shock and aims to promote the standardization of infection management for sepsis and septic shock.

Right patients: rapid screening and early diagnosis

Right patients means patients with sepsis or septic shock. Diagnosing sepsis can be difficult because its signs and symptoms can be caused by other disorders. However, early diagnosis provides the only opportunity for early treatment. Early, aggressive treatment increases the chance of surviving sepsis.[11-21]

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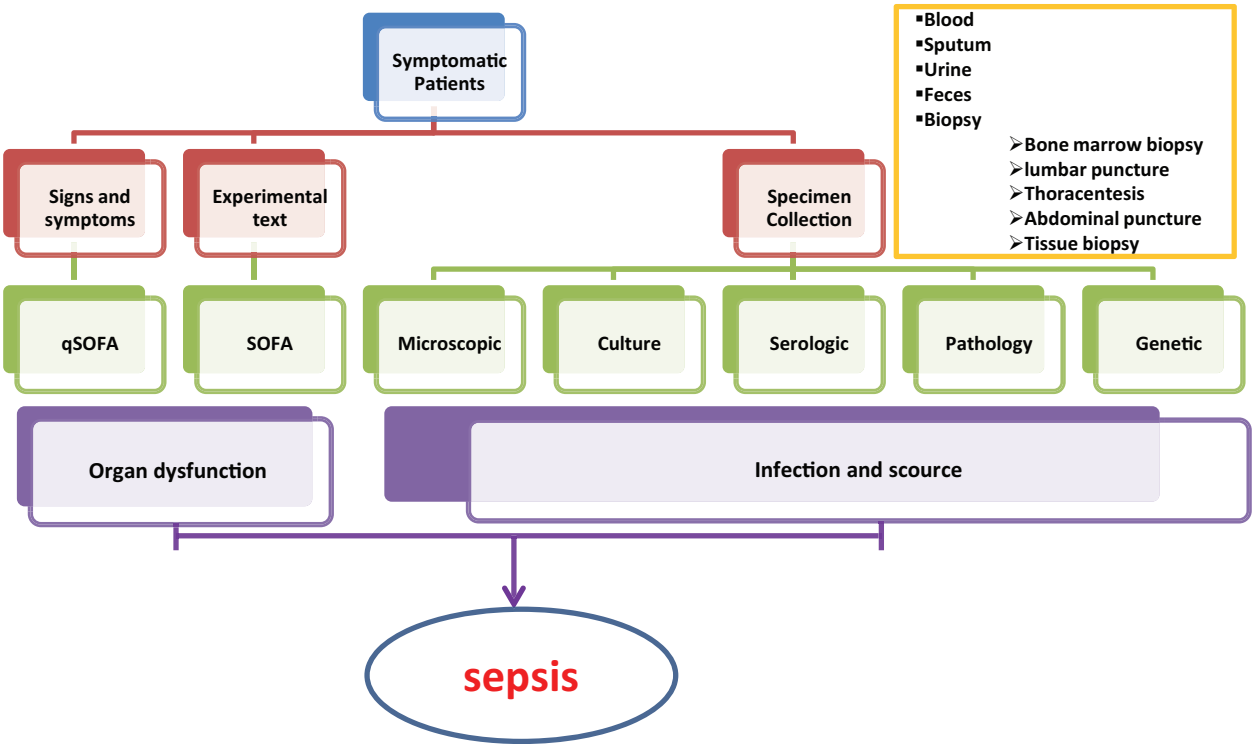

Figure 1: Screening and diagnostic procedures for sepsis and septic shock.

Since the clinical manifestations of infection are not specific, the clinical diagnosis of infection is not easy. For patients with suspected infections, efforts should be made to distinguish them from other non-infectious disease patients. Signs and symptoms vary according to the site and severity of infection. Diagnosis requires a composite of information, including history, physical examination, radiographic findings, and laboratory data. Detailed and accurate medical history, combined with some rapid laboratory methods, for example, biomarkers,[22,23] gene sequencing, rapid microscopy, and radiologic findings, may help establish the diagnosis of infection as early as possible. It must be emphasized that both medical history and examination are essential for the establishment of an infection diagnosis.

The ESICM and the SCCM revised the definition of sepsis and proposed new definitions for sepsis and septic shock (Sepsis-3) in 2016. Sepsis-3 defines sepsis as a "life-threatening organ dysfunction caused by a dysregulated host response to infection." Septic shock refers to a subset of sepsis with severe circulatory, cellular, and metabolic abnormalities that substantially increase mortality.[10] Sepsis-3 clearly defines the correlation between infection and the dysregulated host response and increases the focus on the organ dysfunction caused by this dysregulation. However, there is no gold standard test for diagnosing sepsis. Instead, diagnosis depends on a constellation of clinical signs and symptoms in a patient with suspected infection. The Sequential Organ Failure Assessment (SOFA) score[24] was used to describe the severity of organ dysfunction in Sepsis-3. The score requires several laboratory variables, including PaO_2, platelet count, creatinine level, and bilirubin, for full computation.

Patients with a suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at bedside with the quick SOFA (qSOFA)[25] (ie, altered mental status, systolic blood pressure $\leq$100 mm Hg, or respiratory rate $\geq$22/min). The qSOFA score is less robust than a SOFA score of 2 or greater, but it does not require laboratory tests and can be assessed quickly and repeatedly.[10]

We recommend that hospitals and hospital systems have a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients. Sepsis screening should include early identification of infections and new organ failure. Sepsis screening has been associated with decreased mortality in several studies.[11,26]

Right time: antibiotic therapy, time is life

Right time means the appropriate time to start antibiotic therapy. Early manifestations of sepsis, including shock, the rapid progression of multiple organ failure, and extremely unstable vital signs, will generally draw the attention of medical staff, who often regard shock resuscitation and life support as a life-saving priority. Antibiotic administration, however, is easily ignored. Studies have shown that each 1-h delay in the initiation of effective antibiotic therapy is associated with a significant increase in mortality.[11,19,20,27-30]

Figure 2: The standard flowchart of the new 6Rs rule for anti-infection therapy for sepsis and septic shock. Right patients is the first to be considered. It is necessary to find evidence of the pathogen and conduct appropriate anti-infective treatment in a short period of time. Adequate drainage of infected foci is a key factor. If an infection cannot be clearly identified or drainage cannot be performed effectively, the flowchart principles should be reconsidered to achieve infection treatment and control.

However, controversy has arisen regarding the prompt application of antibiotic therapy. The Infectious Diseases Society of America (IDSA) disagreed with the anti-infection strategies recommended in the 2016 SSC guidelines and published a position statement explaining their opposition in the journal of Clinical Infectious Diseases in November 2017.[31] This statement triggered heated debates in the fields of critical care medicine and infectious disease medicine.

In fact, the IDSA position pursued the accurate diagnosis of affected individuals while ignoring the large population suffering from sepsis who await prompt treatment. Delayed diagnosis and treatment substantially increase the mortality of patients with sepsis. Unfortunately, the diagnosis of infection is far beyond easy. Additionally, research has shown that even if infection is confirmed, the pathogenic microorganism results are not positive in all patients.[32,33]

Of course, a timely diagnosis of infection does not necessarily contradict the accuracy of the diagnosis. To some extent, it is reasonable for the IDSA to expect a more accurate diagnosis of infection. When both the timeliness of anti-infection therapy in patients with sepsis and the goal of an accurate infection diagnosis must be considered, it will inevitably promote the development of new techniques for the rapid clinical diagnosis of infection.

One key factor in determining the success of anti-infection therapy for sepsis is how early we can identify the infection and initiate effective antibiotic therapy within the "golden time."[21] This time is precious for saving critically ill patients and is a key reflection of treatment quality. The

2018 SSC guideline update defined "time of presentation" as "the time of triage in the emergency department or, if referred from another care location, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock, ascertained through chart review."

The development and clinical application of more rapid blood tests based on electronic vital sign and organ function warnings and rapid screening methods, including procalcitonin detection, (1,4)-beta-D-glucan (G) or galactomannan (GM) tests and polymerase chain reaction techniques, not only enable the early diagnosis of patients with sepsis[34-38] but significantly improve the ability to confirm the infectious agent and select appropriate antibiotics.[39,40] With developments and improvements in technology, genomics and genetic testing have greatly enhanced the speed and sensitivity of pathogen screening.[41-44] Now, pathogen gene sequencing technology can be applied in the clinic to aid the clinician in identifying bacterial infections or complex bacterial infections.

Right target: identifying the correct infection source and pathogenic microorganism is the key to successful therapy

Right target means the correct judgment of the infection source and pathogenic microorganism. Source control has a higher priority than antibiotic administration in controlling infection in sepsis and septic shock patients. Pathogenic microorganisms differ greatly depending on the infection source. Additionally, different antibodies are distributed differently among different tissues. Similarly, the techniques used to control or drain the infection sites vary tremendously according to the source. As a result, it is extremely difficult to prescribe antibiotics or formulate a treatment plan for infection control or drainage without identifying the infection source.

The search for underlying pathogenic microorganisms is among the top priorities in anti-infection therapy for sepsis. All of the SSC guidelines, including the 2018 update, emphasize that blood cultures should be collected before antibiotic treatment is initiated.[45-47] In addition to collecting blood cultures, it is equally important to obtain microbiologic specimens from suspected sites of infection, which are determined by the symptoms, physical signs, pathogenesis, and laboratory tests of affected patients during clinical source identification.

It is important to acquire microbial specimens from different sites using site-specific procedures, which are keys to reducing contamination and identifying the actual pathogens. For example, pus and abscess wall tissue specimens obtained through centesis under sterile conditions or aseptic surgical exploration are the most reliable methods for assessing abscesses within the body. On the contrary, in sites such as the lungs, which are naturally nonsterile, the positive pathogen detection rate improves substantially when medical imaging, bronchoscopy examination, and protective brush sampling or bronchoalveolar lavage of the affected lobe are combined. Antibiotic therapy is not required for all bacteria cultured from patient specimens; therefore, correctly distinguishing between colonization and infection is extremely important when planning a rational anti-infection regimen.

Pathogens colonization is the migration of various pathogens from different environments to a certain area of the human body, where they continue to grow and reproduce. Clinically, colonization and infection are often difficult to distinguish. The distinction between colonization and infection should be combined with the location of pathogenic microorganisms, the patient's condition and the characteristics of pathogenic microorganisms. Sometimes it even takes a long follow-up to distinguish between them. A quantitative culture technique is also of great significance for distinguishing pathogens colonization from an infection.

Right antibiotics: rational selection of antibiotics

Right antibiotics means that the antibiotics can accurately combat the pathogenic microorganism. The SSC guidelines recommend the administration of broad-spectrum antibiotics that cover all potential pathogenic microorganisms.[21] Antibiotic therapy should be initiated promptly for patients with sepsis; however, the prognosis will improve only if the right antibiotics are administered.[19,20,48-51] Unfortunately, it is almost impossible to confirm the etiology of sepsis within 1 h of its occurrence. The selection of antibiotics during this period must be empirical.

Therefore, it is crucial to determine the potential pathogenic microorganisms to ensure that the empirical selection of antibiotics is neither unnecessarily strong nor based on entirely groundless decision.[32,52,53] The empirical selection of antibiotics should be completely based on a scientific analysis and the comprehensive judgment of clinical evidence, including age, the anatomic site of infection, symptoms, vital signs, the presence of specific immune defects, the history of antibiotic exposure, microorganism data, and local microorganism epidemiological data, as well as the patient's severity and organ function. For example, in critically ill patients with a hospital-acquired infection, it is not unusual to find extensive drug-resistant or pandrug-resistant bacterial, fungal, or opportunistic infections. Under these circumstances, the strongest antibiotics, such as carbapenems, often turn out to be the least effective. Therefore, recommendations regarding the use of the strongest broad-spectrum antibiotics have so far been nonexistent. The aforementioned clinical data should be taken into account during the prescription of antibiotics. Antibiotics that cover all potential pathogens should be prescribed instead of the stereotypical combination of carbapenems and vancomycin.

It should be emphasized that although empirical antibiotic therapy should be initiated within 1 h of sepsis identification, it should not be continued indefinitely. It should be the goal of every critical care physician to switch from empirical antibiotic therapy to targeted antibiotic therapy when treating patients with sepsis.[54-57] Therefore, it is critical to collect pathogenic microorganism specimens and infection-associated biomarker data prior to initiating antibiotics use and during follow-up treatment. In the meantime, antibiotic therapy should be stopped promptly if infection is excluded.[3,4]

Right dose: optimized application of pharmacokinetics/pharmacodynamics in anti-infection therapy

Right dose means that the dosage of antibiotics is optimized according to the specific antibiotic pharmacokinetic (PK)/pharmacodynamic (PD) changes in sepsis and septic shock patients. In addition to the administration of broad-spectrum antibiotics that cover all likely pathogens, a sufficient amount of antibiotics should be present at the anatomical sites of infection to achieve effective therapy. Under the circumstances of severe infection and septic shock, the concentration of antibiotics is largely influenced by the following aspects: (1) Tissue hypoperfusion: Adequate tissue hypoperfusion is necessary to ensure an adequate therapeutic concentration of antibiotics at the target site. (2) Third-spacing phenomenon: In sepsis and septic shock patients, exotoxins can lead to endothelial damage and thus increased capillary permeability. Capillary leak results in the shifting of fluid from the intravascular space into the interstitial space in a phenomenon described as third spacing. This process increases the volume of distribution of hydrophilic antimicrobials, resulting in lower plasma and tissue antimicrobial concentrations. (3) Hypoproteinemia: Hypoproteinemia is frequently associated with sepsis and septic shock; it leads to the increased plasma level of free antibiotics, which increases the secretion and release of antibiotics.[58] (4) Organ dysfunction: Antibiotic metabolism is altered as a result of organ dysfunction, especially dysfunction of the liver and kidney.[59-62]

Additionally, antibiotic metabolism is substantially altered as a result of treatment: (1) The restoration of body fluid leads to an increased volume of distribution and reduced plasma concentration of antibiotics. (2) Improved tissue perfusion leads to enhanced drug metabolism and excretion. (3) Augmented renal clearance is condition associated with severe sepsis and septic shock that is caused by a hypermetabolic condition along with fluid restoration and the application of vasoactive drugs. These conditions increase the glomerular filtration rate and renal creatinine clearance, which eventually increases the clearance of renally eliminated antibiotics. Sepsis and septic shock patients thus possess a higher renal clearance capability than that suggested by renal creatinine levels.[63-65] Additionally, the restoration of liver function substantially increases the clearance rate of antibiotics through the liver, leading to reduced tissue and plasma concentrations and a shortened half-life of antibiotics.

Different antibiotics also possess different PK and PD characteristics. In terms of PK, there are water-soluble and lipid-soluble antibiotics, and different antibiotics have different protein binding rates, different metabolic models and pathways, different tissue distributions, and different half-lives. In terms of PD, different antibiotics have different pathogen minimum inhibitory concentrations (MICs), and some are time dependent, while others are dose dependent.

The best anti-infection outcome can only be achieved when antibiotics use is optimized based on the distinct pathophysiologic alterations of patients with sepsis and the specific PK/PD characteristics of the antibiotic.[66] For example, the anti-infection effect of concentration-dependent antibiotics depends on the peak concentration,[67-71] while for time-dependent antibiotics, antimicrobial activity relies on the duration of drug exposure as long as the concentration is maintained above the MIC.[72-75] When the blood concentration is more than 4 to 5 times the MIC, the antibiotic's anti-infection effect reaches a plateau, and further increasing the plasma concentration no longer improves the anti-infection effect. Clinical efficacy can be improved by ensuring that $T > MIC$ for these types of antibiotics.

Effective plasma and tissue concentrations of antibiotics are critical for clinical infection control. However, it is important to avoid drug-induced adverse effects under conditions of organ dysfunction. Therefore, it is necessary to quantitatively monitor therapeutic efficacy and drug toxicity. Through such quantitative monitoring and feedback, we may be able to sustain a continuous and dynamic process of targeted antibiotic therapy similar to hemodynamic therapy. Thus, therapeutic drug monitoring (TDM) for antibiotic treatment may be a solution that both assures antibiotic efficacy and avoids drug-related adverse side effects.[62,76-78] TDM-guided antibiotic therapy will become a trend for critically ill patients in the future,[79] as noted in the SSC guidelines.[3,4]

Right source control: controlling the source of infection is vital to anti-infection therapy for sepsis

Right source control means drainage of infected foci by surgery, puncture or other means.[80,81] Source control is critical for managing infection and shock resuscitation.[82-88] For many infectious foci that require drainage, many physicians believe that surgery should only be performed when patients are relatively stable to avoid risks and damage resulting from surgery. These physicians believe that surgery may accelerate patient death and that patients may even die during surgery if the general situation is not corrected. This concern may sound reasonable at first. However, it is important to distinguish between selective surgery and emergency surgery. Studies have shown that as soon as the infectious foci that cause sepsis and require surgery are confirmed, as in cases of intra-abdominal abscess, gastrointestinal perforation, acute suppurative cholangitis, acute pyelonephritis associated with abscess, intestinal ischemia, empyema or septic arthritis, the immediate control of infectious foci is more important than antibiotic administration for managing infection.[80,84,89-94] In fact, failure to control infectious foci will irreversibly aggravate septic shock.[95] Therefore, source control is fundamental to successful shock resuscitation and is considered emergency surgery for these patients.[96,97] In the meantime, rigorous resuscitation prior to and during surgery is important for ensuring that surgery is successful. As a result, the SSC guidelines recommend the drainage of infectious foci within 12 h after diagnosis.[3] Similar to the fact that the earlier resuscitation begins, the more likely it will be successful, it is better to initiate surgical source control as soon as possible. In contrast, if surgery is delayed, the risks of surgery greatly increase as a result of the aggravation of septic shock, and in some cases, surgery becomes impossible, leading to the patient death.

Even for some infectious foci that cannot be eradicated, such as the most common lung infections, adequate sputum drainage is far more important than antibiotics for the control of pneumonia. Inadequate sputum drainage often leads to prolonged pneumonia, which further leads to a double or even triple secondary infection, the prevalence of drug-resistant bacteria and persistent disease. Therefore, insufficient drainage of infectious foci is one of the most important causes of prolonged antibiotic administration and the formation of drug-resistant bacteria.

Summary

Anti-infection therapy is critical to the successful treatment of sepsis. This article proposed a 6Rs rule for anti-infection therapy for sepsis, with the aim of establishing a rigorous and scientifically based clinical therapeutic procedure that encompasses rational decisions regarding the timing of treatment, the identification of the correct pathogen, the selection of appropriate antibiotics, the formulation of a scientifically based antibiotic dosage regimen and the adequate control of infectious foci. This rule will have a positive impact on improving infection control in patients with sepsis.

Conflicts of interest

None.

References

1. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, *et al*. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858–873. doi: 10.1097/01.CCM.0000117317.18092.E4.
2. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, *et al*. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296–327. doi: 10.1097/01.CCM.0000298158.12101.41.
3. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al*. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580–637. doi: 10.1097/CCM.0b013e31827e83af.
4. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, *et al*. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017;45:486–552. doi: 10.1097/CCM.0000000000002255.
5. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Crit Care Med 2018;46:997–1000. doi: 10.1097/CCM.0000000000003119.
6. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348:1546–1554. doi: 10.1056/NEJMoa022139.
7. Linde-Zwirble WT, Angus DC. Severe sepsis epidemiology: sampling, selection, and society. Crit Care 2004;8:222–226. doi: 10.1186/cc2917.
8. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med 2007;35:1244–1250. doi: 10.1097/01.CCM.0000261890.41311.E9.
9. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369:840–851. doi: 10.1056/NEJMra1208623.
10. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315:801–810. doi: 10.1001/jama.2016.0287.
11. Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, *et al*. The surviving sepsis campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Crit Care Med 2010;38:367–374. doi: 10.1097/CCM.0b013e3181cb0cdc.
12. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, *et al*. Surviving sepsis campaign: association between performance metrics and outcomes in a 7.5-year study. Crit Care Med 2015;43:3–12. doi: 10.1097/ccm.0000000000000723.
13. Levy MM, Pronovost PJ, Dellinger RP, Townsend S, Resar RK, Clemmer TP, *et al*. Sepsis change bundles: converting guidelines into meaningful change in behavior and clinical outcome. Crit Care Med 2004;32:S595–S597. doi: 10.1097/01.CCM.0000147016.53607.C4.
14. Damiani E, Donati A, Serafini G, Rinaldi L, Adrario E, Pelaia P, *et al*. Effect of performance improvement programs on compliance with sepsis bundles and mortality: a systematic review and meta-analysis of observational studies. PLoS One 2015;10:e0125827. doi: 10.1371/journal.pone.0125827.
15. Rhodes A, Phillips G, Beale R, Cecconi M, Chiche JD, De Backer D, *et al*. The surviving sepsis campaign bundles and outcome: results from the International Multicentre Prevalence Study on Sepsis (the IMPreSS study). Intensive Care Med 2015;41:1620–1628. doi: 10.1007/s00134-015-3906-y.
16. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, *et al*. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med 2017;376:2235–2244. doi: 10.1056/NEJMoa1703058.
17. Liu VX, Morehouse JW, Marelich GP, Soule J, Russell T, Skeath M, *et al*. Multicenter implementation of a treatment bundle for patients with sepsis and intermediate lactate values. Am J Respir Crit Care Med 2016;193:1264–1270. doi: 10.1164/rccm.201507-1489OC.
18. Leisman DE, Doerfler ME, Ward MF, Masick KD, Wie BJ, Gribben JL, *et al*. Survival benefit and cost savings from compliance with a simplified 3-hour sepsis bundle in a series of prospective, multisite, observational cohorts. Crit Care Med 2017;45:395–406. doi: 10.1097/ccm.0000000000002184.
19. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, *et al*. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014;42:1749–1755. doi: 10.1097/ccm.0000000000000330.
20. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, *et al*. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589–1596. doi: 10.1097/01.CCM.0000217961.75225.E9.
21. Kumar A. Systematic bias in meta-analyses of time to antimicrobial in sepsis studies. Crit Care Med 2016;44:e234–235. doi: 10.1097/CCM.0000000000001512.
22. Ghabra H, White W, Townsend M, Boysen P, Nossaman B. Use of biomarkers in the prediction of culture-proven infection in the surgical intensive care unit. J Crit Care 2019;49:149–154. doi: 10.1016/j.jcrc.2018.10.023.
23. Sungurlu S, Balk RA. The role of biomarkers in the diagnosis and management of pneumonia. Clin Chest Med 2018;39:691–701. doi: 10.1016/j.ccm.2018.07.004.
24. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, *et al*. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–710.
25. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, *et al*. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315:762–774. doi: 10.1001/jama.2016.0288.
26. Jones SL, Ashton CM, Kiehne L, Gigliotti E, Bell-Gordon C, Disbot M, *et al*. Reductions in sepsis mortality and costs after design and implementation of a nurse-based early recognition and response program. Jt Comm J Qual Patient Saf 2015;41:483–491. doi: 10.1016/S1553-7250(15)41063-3.
27. O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, *et al*. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recomm Rep 2002;51:1–29.
28. Ferrer R, Artigas A, Suarez D, Palencia E, Levy MM, Arenzana A, *et al*. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. Am J Respir Crit Care Med 2009;180:861–866. doi: 10.1164/rccm.200812-1912OC.
29. Liu VX, Fielding-Singh V, Greene JD, Baker JM, Iwashyna TJ, Bhattacharya J, *et al*. The timing of early antibiotics and hospital

mortality in sepsis. Am J Respir Crit Care Med 2017;196:856–863. doi: 10.1164/rccm.201609-1848OC.
30. Whiles BB, Deis AS, Simpson SQ. Increased time to initial antimicrobial administration is associated with progression to septic shock in severe sepsis patients. Crit Care Med 2017;45:623–629. doi: 10.1097/CCM.0000000000002262.
31. IDSA Sepsis Task Force. Infectious Diseases Society of America (IDSA) POSITION STATEMENT: Why IDSA Did Not Endorse the Surviving Sepsis Campaign Guidelines. Clin Infect Dis 2018;66:1631–1635. doi: 10.1093/cid/cix997.
32. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, *et al*. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 2009;136:1237–1248. doi: 10.1378/chest.09-0087.
33. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, *et al*. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699–709. doi: 10.1056/nejm200103083441001.
34. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, *et al*. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis 2016;16:819–827. doi: 10.1016/S1473-3099(16)00053-0.
35. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, *et al*. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010;375:463–474. doi: 10.1016/S0140-6736(09)61879-1.
36. Wheat LJ. Approach to the diagnosis of invasive aspergillosis and candidiasis. Clin Chest Med 2009;30:367–377. viii. doi: 10.1016/j.ccm.2009.02.012.
37. Mylonakis E, Clancy CJ, Ostrosky-Zeichner L, Garey KW, Alangaden GJ, Vazquez JA, *et al*. T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. Clin Infect Dis 2015;60:892–899. doi: 10.1093/cid/ciu959.
38. Lucignano B, Ranno S, Liesenfeld O, Pizzorno B, Putignani L, Bernaschi P, *et al*. Multiplex PCR allows rapid and accurate diagnosis of bloodstream infections in newborns and children with suspected sepsis. J Clin Microbiol 2011;49:2252–2258. doi: 10.1128/JCM.02460-10.
39. Aguado JM, Vazquez L, Fernandez-Ruiz M, Villaescusa T, Ruiz-Camps I, Barba P, *et al*. Serum galactomannan versus a combination of galactomannan and polymerase chain reaction-based Aspergillus DNA detection for early therapy of invasive aspergillosis in high-risk hematological patients: a randomized controlled trial. Clin Infect Dis 2015;60:405–414. doi: 10.1093/cid/ciu833.
40. Hou TY, Wang SH, Liang SX, Jiang WX, Luo DD, Huang DH. The screening performance of serum 1,3-beta-D-glucan in patients with invasive fungal diseases: a meta-analysis of prospective cohort studies. PLoS One 2015;10:e0131602. doi: 10.1371/journal.pone.0131602.
41. Ashikawa S, Tarumoto N, Imai K, Sakai J, Kodana M, Kawamura T, *et al*. Rapid identification of pathogens from positive blood culture bottles with the MinION nanopore sequencer. J Med Microbiol 2018;67:1589–1595. doi: 10.1099/jmm.0.000855.
42. Watanabe N, Kryukov K, Nakagawa S, Takeuchi JS, Takeshita M, Kirimura Y, *et al*. Detection of pathogenic bacteria in the blood from sepsis patients using 16S rRNA gene amplicon sequencing analysis. PLoS One 2018;13:e0202049. doi: 10.1371/journal.pone.0202049.
43. Long Y, Zhang Y, Gong Y, Sun R, Su L, Lin X, *et al*. Diagnosis of sepsis with cell-free DNA by next-generation sequencing technology in ICU patients. Arch Med Res 2016;47:365–371. doi: 10.1016/j.arcmed.2016.08.004.
44. Leitner E, Kessler HH. Broad-range PCR for the identification of bacterial and fungal pathogens from blood: a sequencing approach. Methods Mol Biol 2015;1237:129–138. doi: 10.1007/978-1-4939-1776-1_13.
45. Zadroga R, Williams DN, Gottschall R, Hanson K, Nordberg V, Deike M, *et al*. Comparison of 2 blood culture media shows significant differences in bacterial recovery for patients on antimicrobial therapy. Clin Infect Dis 2013;56:790–797. doi: 10.1093/cid/cis1021.
46. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. Pediatrics 2001;108:1169–1174.
47. Cardoso T, Carneiro AH, Ribeiro O, Teixeira-Pinto A, Costa-Pereira A. Reducing mortality in severe sepsis with the implementation of a core 6-hour bundle: results from the Portuguese community-acquired sepsis study (SACiUCI study). Crit Care (London, England) 2010;14:R83. doi: 10.1186/cc9008.
48. Barie PS, Hydo LJ, Shou J, Larone DH, Eachempati SR. Influence of antibiotic therapy on mortality of critical surgical illness caused or complicated by infection. Surg Infect 2005;6:41–54. doi: 10.1089/sur.2005.6.41.
49. Barochia AV, Cui X, Vitberg D, Suffredini AF, O'Grady NP, Banks SM, *et al*. Bundled care for septic shock: an analysis of clinical trials. Crit Care Med 2010;38:668–678. doi: 10.1097/CCM.0b013e3181cb0ddf.
50. Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, *et al*. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 2010;38:1045–1053. doi: 10.1097/CCM.0b013e3181cc4824.
51. Sherwin R, Winters ME, Vilke GM, Wardi G. Does early and appropriate antibiotic administration improve mortality in emergency department patients with severe sepsis or septic shock? J Emerg Med 2017;53:588–595. doi: 10.1016/j.jemermed.2016.12.009.
52. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 2000;118:146–155. doi: 10.1378/chest.118.1.146.
53. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother 2010;54:4851–4863. doi: 10.1128/aac.00627-10.
54. Pollack LA, van Santen KL, Weiner LM, Dudeck MA, Edwards JR, Srinivasan A. Antibiotic stewardship programs in U.S. acute care hospitals: findings from the 2014 national healthcare safety network annual hospital survey. Clin Infect Dis 2016;63:443–449. doi: 10.1093/cid/ciw323.
55. Garnacho-Montero J, Gutierrez-Pizarraya A, Escoresca-Ortega A, Corcia-Palomo Y, Fernandez-Delgado E, Herrera-Melero I, *et al*. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. Intensive Care Med 2014;40:32–40. doi: 10.1007/s00134-013-3077-7.
56. Weiss CH, Persell SD, Wunderink RG, Baker DW. Empiric antibiotic, mechanical ventilation, and central venous catheter duration as potential factors mediating the effect of a checklist prompting intervention on mortality: an exploratory analysis. BMC Health Serv Res 2012;12:198. doi: 10.1186/1472-6963-12-198.
57. Guo Y, Gao W, Yang H, Ma C, Sui S. De-escalation of empiric antibiotics in patients with severe sepsis or septic shock: a meta-analysis. Heart Lung 2016;45:454–459. doi: 10.1016/j.hrtlng.2016.06.001.
58. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, *et al*. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 2014;14:498–509. doi: 10.1016/s1473-3099(14)70036-2.
59. Chelluri L, Jastremski MS. Inadequacy of standard aminoglycoside loading doses in acutely ill patients. Crit Care Med 1987;15:1143–1145. doi: 10.1097/00003246-198712000-00015.
60. Pletz MW, Bloos F, Burkhardt O, Brunkhorst FM, Bode-Boger SM, Martens-Lobenhoffer J, *et al*. Pharmacokinetics of moxifloxacin in patients with severe sepsis or septic shock. Intensive Care Med 2010;36:979–983. doi: 10.1007/s00134-010-1864-y.
61. van Zanten AR, Polderman KH, van Geijlswijk IM, van der Meer GY, Schouten MA, Girbes AR. Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study. J Crit Care 2008;23:422–430. doi: 10.1016/j.jcrc.2007.11.011.
62. Blot S, Koulenti D, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, *et al*. Does contemporary vancomycin dosing achieve therapeutic targets in a heterogeneous clinical cohort of critically ill patients? Data from the multinational DALI study. Crit Care (London England) 2014;18:R99. doi: 10.1186/cc13874.
63. Baptista JP, Sousa E, Martins PJ, Pimentel JM. Augmented renal clearance in septic patients and implications for vancomycin optimisation. Int J Antimicrob Agents 2012;39:420–423. doi: 10.1016/j.ijantimicag.2011.12.011.
64. Hobbs AL, Shea KM, Roberts KM, Daley MJ. Implications of augmented renal clearance on drug dosing in critically ill patients: a

focus on antibiotics. Pharmacotherapy 2015;35:1063–1075. doi: 10.1002/phar.1653.
65. Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BC, Ungerer JP, *et al*. Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 2012;142:30–39. doi: 10.1378/chest.11-1671.
66. Moore RD, Smith CR, Lietman PS. Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. Am J Med 1984;77:657–662. doi: 10.1016/0002-9343(84)90358-9.
67. Dorman T, Swoboda S, Zarfeshenfard F, Trentler B, Lipsett PA. Impact of altered aminoglycoside volume of distribution on the adequacy of a three milligram per kilogram loading dose. Critical Care Research Group. Surgery 1998;124:73–78. doi: 10.1016/S0039-6060(98)70077-7.
68. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993;37:1073–1081. doi: 10.1128/AAC.37.5.1073.
69. Preston SL, Drusano GL, Berman AL, Fowler CL, Chow AT, Dornseif B, *et al*. Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. JAMA 1998;279:125–129. doi: 10.1001/jama.279.2.125.
70. Drusano GL, Preston SL, Fowler C, Corrado M, Weisinger B, Kahn J. Relationship between fluoroquinolone area under the curve: minimum inhibitory concentration ratio and the probability of eradication of the infecting pathogen, in patients with nosocomial pneumonia. J Infect Dis 2004;189:1590–1597. doi: 10.1086/383320.
71. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother 1999;43:623–629.
72. Schentag JJ, Smith IL, Swanson DJ, DeAngelis C, Fracasso JE, Vari A, *et al*. Role for dual individualization with cefmenoxime. Am J Med 1984;77:43–50. doi: 10.1016/S0002-9343(84)80074-1.
73. Crandon JL, Bulik CC, Kuti JL, Nicolau DP. Clinical pharmacodynamics of cefepime in patients infected with Pseudomonas aeruginosa. Antimicrob Agents Chemother 2010;54:1111–1116. doi: 10.1128/aac.01183-09.
74. McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T > MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 2008;31:345–351. doi: 10.1016/j.ijantimicag.2007.12.009.
75. Roberts JA, Abdul-Aziz MH, Davis JS, Dulhunty JM, Cotta MO, Myburgh J, *et al*. Continuous versus intermittent beta-lactam infusion in severe sepsis. A meta-analysis of individual patient data from randomized trials. Am J Respir Crit Care Med 2016;194:681–691. doi: 10.1164/rccm.201601-0024OC.
76. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, *et al*. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014;58:1072–1083. doi: 10.1093/cid/ciu027.
77. Taccone FS, Laterre PF, Spapen H, Dugernier T, Delattre I, Layeux B, *et al*. Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock. Crit Care (London, England) 2010;14:R53. doi: 10.1186/cc8945.
78. Rea RS, Capitano B, Bies R, Bigos KL, Smith R, Lee H. Suboptimal aminoglycoside dosing in critically ill patients. Ther Drug Monit 2008;30:674–681. doi: 10.1097/FTD.0b013e31818b6b2f.
79. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. Clin Infect Dis 1997;24:796–809. doi: 10.1093/clinids/24.5.796.
80. Jimenez MF, Marshall JC, International Sepsis F. Source control in the management of sepsis. Intensive Care Med 2001;27 (Suppl 1): S49–S62. doi: 10.1007/PL00003797.
81. Oliver ZP, Perkins J. Source Identification and Source Control. Emerg Med Clin North Am 2017;35:43–58. doi: 10.1016/j.emc.2016.08.005.
82. Azuhata T, Kinoshita K, Kawano D, Komatsu T, Sakurai A, Chiba Y, *et al*. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. Crit Care (London, England) 2014;18:R87. doi: 10.1186/cc13854.
83. Bloos F, Thomas-Ruddel D, Ruddel H, Engel C, Schwarzkopf D, Marshall JC, *et al*. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. Crit Care (London, England) 2014;18:R42. doi: 10.1186/cc13755.
84. Moss RL, Musemeche CA, Kosloske AM. Necrotizing fasciitis in children: prompt recognition and aggressive therapy improve survival. J Pediatr Surg 1996;31:1142–1146. doi: 10.1016/S0022-3468(96)90104-9.
85. Wong CH, Chang HC, Pasupathy S, Khin LW, Tan JL, Low CO. Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. J Bone Joint Surg Am 2003;85-a:1454–1460.
86. Chao WN, Tsai CF, Chang HR, Chan KS, Su CH, Lee YT, *et al*. Impact of timing of surgery on outcome of *Vibrio vulnificus*-related necrotizing fasciitis. Am J Surg 2013;206:32–39. doi: 10.1016/j.amjsurg.2012.08.008.
87. Buck DL, Vester-Andersen M, Moller MH. Surgical delay is a critical determinant of survival in perforated peptic ulcer. Br J Surg 2013;100:1045–1049. doi: 10.1002/bjs.9175.
88. Karvellas CJ, Abraldes JG, Zepeda-Gomez S, Moffat DC, Mirzanejad Y, Vazquez-Grande G, *et al*. The impact of delayed biliary decompression and anti-microbial therapy in 260 patients with cholangitis-associated septic shock. Aliment Pharmacol Ther 2016;44:755–766. doi: 10.1111/apt.13764.
89. Hadley GP. Intra-abdominal sepsis–epidemiology, aetiology and management. Semin Pediatr Surg 2014;23:357–362. doi: 10.1053/j.sempedsurg.2014.06.008.
90. Boyer A, Vargas F, Coste F, Saubusse E, Castaing Y, Gbikpi-Benissan G, *et al*. Influence of surgical treatment timing on mortality from necrotizing soft tissue infections requiring intensive care management. Intensive Care Med 2009;35:847–853. doi: 10.1007/s00134-008-1373-4.
91. Bufalari A, Giustozzi G, Moggi L. Postoperative intraabdominal abscesses: percutaneous versus surgical treatment. Acta Chir Belg 1996;96:197–200.
92. Tellor B, Skrupky LP, Symons W, High E, Micek ST, Mazuski JE. Inadequate source control and inappropriate antibiotics are key determinants of mortality in patients with intra-abdominal sepsis and associated bacteremia. Surg Infect 2015;16:785–793. doi: 10.1089/sur.2014.166.
93. Vogler Jt , Hart L, Holmes S, Sciaretta J, Davis JM. Rapid source-control laparotomy: is there a mortality benefit in septic shock? Surg Infect 2018;19:225–229. doi: 10.1089/sur.2017.191.
94. Rausei S, Pappalardo V, Ruspi L, Colella A, Giudici S, Ardita V, *et al*. Early versus delayed source control in open abdomen management for severe intra-abdominal infections: a retrospective analysis on 111 cases. World J Surg 2018;42:707–712. doi: 10.1007/s00268-017-4233-y.
95. Opal SM. Source control in sepsis urgent or not so fast? Crit Care Med 2017;45:130–132. doi: 10.1097/CCM.0000000000002123.
96. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, *et al*. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect 2010;11:79–109. doi: 10.1089/sur.2009.9930.
97. Sartelli M, Chichom-Mefire A, Labricciosa FM, Hardcastle T, Abu-Zidan FM, Adesunkanmi AK, *et al*. The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg 2017;12:29. doi: 10.1186/s13017-017-0141-6.

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