

Infectious Diseases Society of America (IDSA) POSITION STATEMENT: Why IDSA Did Not Endorse the Surviving Sepsis Campaign Guidelines

IDSA Sepsis Task Force*

IDSA did not endorse the 2016 Surviving Sepsis Campaign Guidelines despite being represented in the working group that drafted the guidelines document. Leadership from the IDSA, the Surviving Sepsis Campaign Guidelines, and the Society of Critical Care Medicine had numerous amicable discussions primarily regarding the bolded, rated guidelines recommendations. Our societies had different perspectives, however, regarding the interpretation of the major studies that informed the guidelines' recommendations, thus leading us to different conclusions and different perspectives on the recommendations. IDSA consequently elected not to endorse the guidelines. IDSA nonetheless hopes to be able to continue collaborating with the Surviving Sepsis Campaign and the Society of Critical Care Medicine to resolve our differences and to develop further strategies together to prevent sepsis and septic shock as well as reduce death and disability from these conditions both nationally and globally.

Keywords. Surviving Sepsis; Guidelines; Endorsement; IDSA.

The 2016 Surviving Sepsis Campaign Guidelines were published under the auspices of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) [1]. After a great deal of deliberation and discussion with SCCM, the Infectious Diseases Society of America (IDSA) reluctantly elected not to endorse these guidelines.

IDSA admires the formidable work the Surviving Sepsis Campaign has done to improve care and outcomes for patients with sepsis and septic shock. The Surviving Sepsis Campaign has raised awareness about sepsis, emphasized the importance of early recognition, and focused attention on the need to treat septic patients aggressively and expeditiously with evidence-based interventions. Nonetheless, IDSA did not agree with many important aspects of the Surviving Sepsis Campaign Guidelines.

The IDSA's delegate to the Surviving Sepsis Campaign's writing committee discussed these differences of opinion with the writing committee, the Surviving Sepsis Campaign leadership, and with the leaders of IDSA and SCCM. Unfortunately, our 2 societies were unable to reach consensus on some of the guidelines' pivotal recommendations and their associated explanatory text within the publication deadline set by the Surviving Sepsis Campaign and SCCM. Thus, the IDSA decided to withhold its

endorsement. This article summarizes some of IDSA's specific concerns.

DISTINGUISHING SEPSIS FROM NONINFECTIOUS SYNDROMES

IDSA's major concern with the guidelines is its failure to acknowledge the practical difficulties clinicians often face when trying to diagnose sepsis. It is often unclear whether or not infection is present and whether or not organ dysfunction is due to infection. Studies suggest that up to 40% of patients admitted to intensive care units with a diagnosis of sepsis do not have an infection and thus do not actually have sepsis [2]. Hence, the benefits of treating patients who are infected need to be balanced against the harms of treating patients who at first appear as if they might have infections but in fact do not.

The Surviving Sepsis Campaign Guidelines do not differentiate between patients with *suspected sepsis* and *suspected septic shock*. The definitions of *sepsis* and *septic shock* have undergone evolution over the past 15 years, and different documents continue to use different versions of the definitions, which can lead to confusion [3–9]. Unfortunately, none of the iterations of definitions provides optimal sensitivity or specificity. However, regardless of which definitions are used for *sepsis* and *septic shock*, conflating *suspected sepsis* with *suspected septic shock* leads to one-size-fits-all recommendations. If there is a possibility that a patient with shock might have an infection, it is understandable and appropriate to administer broad spectrum antibiotics and fluids immediately. Clearly, if the patient is infected, there is little margin for error. For patients with less severe disease and in whom the presence of infection is uncertain, there is often more time to gather additional diagnostic

Received 1 July 2017; editorial decision 18 October 2017; accepted 8 November 2017; published online November 22, 2017.

*IDSA Sepsis Task Force Members listed in Acknowledgements.

Correspondence: H. Masur, MD, Chief, Critical Care Medicine, Dept Bldg 10, Rm 2C145, 10 Center Dr, MSC 1662, Bethesda, MD 20892-1662 (hmasur@nih.gov).

Clinical Infectious Diseases® 2018;66(10):1631–5

Published by Oxford University Press for the Infectious Diseases Society of America 2017. This work is written by (a) US Government employee(s) and is in the public domain in the US. DOI: 10.1093/cid/cix997

data to generate a more informed and precise therapeutic plan. If the clinician decides that infection is plausible, antibiotics can and should be administered promptly [10, 11]. In many cases, however, patients that initially seemed as if they might be infected turn out to have noninfectious conditions, or infections that do not benefit from antibacterial agents, for example, viral infections. Such patients stand only to suffer potential harm from antibiotics. Moreover, overuse of antibiotics has negative consequences for hospital populations in general in addition to the specific patient receiving treatment. This risk is worth taking for a patient in shock, but we do not believe the risk should be entered lightly in patients with less severe illness where there is often time to gather more data before committing the patient to antibiotics.

TIME TO INITIATION OF EMPIRIC ANTIBIOTIC THERAPY

Employers and health plans rightfully turn to professional guidelines when developing quality measures. Unfortunately this can become problematic when guideline recommendations are overly rigid [12]. The Surviving Sepsis Campaign Guidelines recommend “that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 hour for both sepsis and septic shock (strong recommendation, moderate quality of evidence; grade applies to both conditions).”

IDSA agrees that antimicrobials should be initiated as soon as possible to patients with severe infections. We are fearful, however, that stipulating an aggressive, fixed time period “from the time of recognition” may lead to unintended consequences, namely, an increased likelihood that broad-spectrum antibiotics will be given more frequently to uninfected patients with syndromes that look like infections in the rush to meet the fixed frame stipulated for infected patients.

Several of the senior authors of Surviving Sepsis Campaign Guidelines published an explanatory article regarding the 2016 Surviving Sepsis Campaign Guidelines that states: “First, the recommendation for antibiotic administration within an hour of diagnosis of sepsis is a lofty goal of care, judged to be ideal for the patient but not yet standard care ... This is one among several ‘aspirational recommendations’ considered by the experts to represent best practice that individual practitioners and healthcare teams should strive to operationalize” [13]. Of note, other guidelines or bundles from CMS [7] and Institute for Healthcare Quality Improvement [8, 9] propose that 3 hours is a reasonable target.

None of these organizations, however, including the Surviving Sepsis Campaign Guidelines, provide clear guidance on precisely how to measure adherence. To adhere to best practices recommended by the guidelines, providers need specific directions. The guidelines do not define how “time to antibiotics” is measured in terms of either a starting point or the endpoint. There are several possible starting points such as time of first fever documented by vital signs, time of first health care

provider contact, time of emergency room admission, time to positive sepsis screening, time of first documentation of organ dysfunction, or time of first antibiotic order. Similarly, there are many possible measured endpoints such as time to initiation of first antibiotic, time to initiation of all antibiotics, or time to initiation of appropriate antibiotics. Regulatory agencies might thus make their own definitions. Individual hospitals might advertise their quality by making their own easily attained parameters and showing better performance than comparator organizations that use more stringent definitions.

We agree in principle with the desirability of “prompt” administration of antibiotics for documented or suspected infection. Analogous to hypertension, one might consider *sepsis* to be a medical urgency, and *septic shock* to be a medical emergency. Unfortunately, however, unlike severe hypertension, myocardial infarct, or stroke, there is no objective event, electrocardiogram, or vital sign that would define sepsis or septic shock with any specificity.

We do think it is feasible and constructive to propose a recommendation that is easily measured and likely to improve care, that is, a recommendation that encourages acceleration of antibiotic delivery. Thus the emphasis would be on accelerating drug delivery once the clinician makes the decision that antibiotics are appropriate and writes a stat order and removes emphasis on recognition that might be interpreted as time of emergency room registration, time of first fever, etc. Such a recommendation is supported by observational data: “*For patients with presumed sepsis or septic shock, the administration of each antibiotic ordered should be initiated promptly, with health care systems working to reduce that time to as short a duration as feasible*” [10, 14–17]. We currently would not define whether “promptly” should be interpreted as 1 hour, 2 hours, 3 hours, or something else until a comprehensive review by stakeholders to assess the feasibility of implementation [18, 19]. Thus, for patients who appear to be in septic shock, the provider would optimally make a rapid assessment, recognize that starting antibiotics is an emergency, and signal the healthcare team of this need by entering a stat order. Pharmacy and nursing in turn would collaborate to assure that antibiotics are immediately available and immediately administered, working to reduce the measured time from order placement to initiation of administration for each and every antibiotic. For a patient who appeared to be septic but was not in shock, the provider might choose to obtain additional or even sequential data to determine if infection were in fact the inciting cause. If the assessment was that antibiotics were needed for this medical urgency, the healthcare team would then ensure that each and every stat antibiotic ordered was promptly administered.

BLOOD CULTURES AND IV ACCESS CATHETERS

The identification of the organism causing sepsis or septic shock is obviously an important part of any set of guidelines for

clinicians because such identification is pivotal for administering optimal therapeutic interventions. For diagnostic tests that have been in use for many years, a standard approach to documenting the cause of sepsis or septic shock has been to draw blood cultures, as well as to perform diagnostic studies on other appropriate fluids and tissues. The guidelines endorse drawing at least two blood cultures before starting antimicrobial therapy, including one blood culture drawn peripherally and one drawn through an intravenous catheter. This seems eminently reasonable. However, the information recommending two cultures is relegated to a bolded “Remark” that is not rated, and information about drawing blood cultures from a peripheral site plus one (or all) catheters is buried in subsequent text. The guidelines do not address whether to draw blood cultures from all catheters and all lumens, or how to prioritize catheters if there are multiple catheters and lumens in place. Later in the document the guidelines provide advice about removing catheters if such devices are “a possible” source of infection. However, in a septic patient with a catheter, especially a catheter that has been in place for several days and used multiple times, isn’t the catheter always a “possible” source? In addition, clinicians are given little guidance about tunnel infection, exit infection, or strategies for removal of implanted or temporary devices. We think the guidelines should have clearly recommended removing catheters in patients with refractory shock, hard to treat organisms, or persistent bacteremia. Readers could be referred to other sources, but experience suggests that having pivotal information in one place maximizes the likelihood that such information will be accessed [20].

COMBINATION AND MULTIDRUG THERAPY

A major contribution of these guidelines should be advice on which antimicrobial agents to choose for empiric and for targeted therapy. The classification and terminology of antimicrobial therapy (Table 6) in the document is confusing. The distinction between multidrug and combination therapy is probably not obvious to either casual readers of the document or even to those who carefully read Table 6. This table provides definitions for “empiric,” “targeted/definitive,” “multi-drug,” and “combination” therapy. These are not widely held definitions, and their distinction between combination therapy (2 or more active agents prescribed to accelerate pathogen clearance rather than to broaden antimicrobial coverage), and multidrug therapy (therapy with multiple antimicrobials to broaden coverage for empiric therapy or to accelerate pathogen clearance, includes combination therapy) would not be obvious to many readers or even to some experts in the field. In many sentences that discuss therapy, the term “combination” therapy is used when, in fact, with their definitions, they should be using the term “multidrug” therapy.

The guidelines suggest that treating septic shock with 2 antibiotics, both active against a patient’s known pathogens,

for “several days” is likely to be clinically useful. They recommend continuing combination therapy with 2 active agents until there is clinical improvement and/or evidence of infection resolution, regardless of when susceptibility results return. We do not believe that there are robust data to support these recommendations [21, 22]. We believe the available data support the empiric use of 2 agents active against gram-negative bacilli for empiric treatment of septic shock in order to increase the chance of having at least one active agent administered. Once susceptibilities return, however, and demonstrate that there is at least one active agent with published evidence for clinical benefit, we believe the available data suggest there is no evidence to support continuing 2 gram-negative agents as opposed to using one active agent. Indeed one section of the guidelines advocates “that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted...” only to apparently be contradicted subsequently: “several days of combination therapy is biologically plausible and is likely to be clinically useful.”

Indeed, the concept of “combination therapy” as defined in this document is troubling. The guidelines define “combination therapy” as multidrug regimens that accelerate pathogen clearance, inhibit toxin production, or provide immunomodulatory effects. The evidence for the hypothesis that “combination therapy” accelerates pathogen clearance is controversial in situations where a highly susceptible pathogen can be treated with a single highly active agent. The guidelines cite an observational propensity-matched analysis and meta-analysis/meta-regression analyses to support this approach [23–34], but there were substantial limitations to these 2 studies as described in details elsewhere [21]. A randomized controlled trial [33] of this strategy, however, showed no benefit of combination therapy versus monotherapy for patients with sepsis or septic shock (indeed, there were significantly more adverse effects and a trend toward higher mortality rates in patients with septic shock randomized to combination vs monotherapy) [33]. From a process perspective, it is also less than optimal that a rated statement is placed in the text rather than as a bolded recommendation, even if the recommendation for combination therapy against a sensitive organism is “a weak recommendation based on low quality of evidence.”

Multiple statements within the guidelines imply that most patients with sepsis or septic shock often harbor antimicrobial resistant pathogens. This is not consistent with the available evidence and could encourage clinicians to use more antimicrobial agents than would otherwise be indicated. Multidrug empiric antibiotic therapy is appropriate for patients with risk factors for multidrug-resistant organisms but is not necessarily required upfront for all patients with sepsis, particularly in hospitals with low levels of antimicrobial resistance.

PROCALCITONIN

Biomarkers and molecular tests could be very useful to establish quickly and accurately whether syndromes are caused by infection and, in the case of molecular tests, what the causative organism is and what resistance genes it harbors. The Surviving Sepsis Campaign Guidelines endorses the use of procalcitonin, in accordance with other guidelines [35]. Procalcitonin levels have been shown to rise within 4–6 hours in response to invasive bacterial infection. However, the Surviving Sepsis Campaign Guidelines do not provide specific and evidence-based recommendations that providers can follow. The failure to provide specific guidance leaves readers with the task of finding another source to operationalize the recommendation.

The guidelines indicate that procalcitonin “can be used” in septic patients, but what do the words “can be used” indicate to the clinician because many tests “can be used.” The issue rather is “should they be used?” The guidelines also specifically suggest that procalcitonin is a biomarker that is useful for determining when to stop antibiotics in patients who have “limited evidence of sepsis,” a patient population that is not defined. Our interpretation of the literature is that randomized controlled trials demonstrate that procalcitonin guidance for duration of antibiotic therapy is feasible and safe in critically ill patients *with* infections [36, 37]. We are unaware of data supporting the guidelines’ recommendation to use procalcitonin in patients with “limited evidence of sepsis” even if it were clear what population this refers to.

PHARMACOKINETICS/PHARMACODYNAMICS

The recommendations for optimizing pharmacokinetics and pharmacodynamics are also lacking in specifics. If the Surviving Sepsis Campaign Guidelines deem that there is evidence that prolonged dosing administration of certain antimicrobial agents, for instance, is beneficial, they should indicate to clinicians how to operationalize such an approach, and they should distinguish how to administer stat antibiotics (in some cases a rapid bolus) and how to administer subsequent doses.

PROLONGED PROPHYLAXIS

The Surviving Sepsis Campaign Guidelines recommend against “sustained systemic antimicrobial prophylaxis in patients with severe inflammatory states of noninfectious origin.” This suggests that “nonsustained” antibiotic courses are indicated. IDSA recognizes that there are many situations when empiric therapy is reasonable. However, IDSA believes that if there is no infection, there is no indication for antibiotic therapy. The Surviving Sepsis Campaign’s subsequent text suggests that the authors may actually be referring to infection prevention rather than treatment. Indeed, elsewhere the guidelines suggest “brief antibiotic prophylaxis for specific invasive procedures may be appropriate.” We obviously believe that infection prevention is a critical priority

for all hospitals, but it is a large and complex topic that is already well covered by other dedicated guidelines. The Surviving Sepsis Campaign Guidelines should either refer to these other Guidelines or provide a better description of what aspects of infection prevention and prophylaxis they are referring to.

DURATION OF THERAPY

Lastly, the Surviving Sepsis Campaign recommends treating most patients with sepsis or septic shock with 7–10 days of antibiotics. IDSA believes that is an oversimplified approach and risks treating some infections inadequately and others excessively. This recommendation contradicts the preponderance of evidence from randomized controlled trials, systematic reviews, and guidelines that have shown the safety and efficacy of shorter therapeutic courses for certain infections: 4 days for intra-abdominal infections and abscesses with source control [38]; 5 days for community-acquired pneumonia [39–41], 7 days or less for nosocomial pneumonia [35, 42, 43]; and 7 days or less for acute pyelonephritis [44]. It is difficult for a guideline document to give specific advice on duration of therapy given the complex host and microbial interactions unique to each patient. We would suggest summarizing treatment duration considerations and recommendations per condition rather than trying to establish general recommendations for all different conditions.

CONCLUSION

In conclusion, IDSA had multiple substantial disagreements with the Surviving Sepsis Campaign’s recommendations. We are disappointed that IDSA and SCCM were unable to resolve these issues before the Surviving Sepsis Campaign Guidelines were released. We hope we will be able to collaborate with SCCM and the Surviving Sepsis Campaign to find common ground for future guidelines. The IDSA strongly believes that patients and healthcare providers are best served if professional societies can speak with one voice on topics that are shared across specialties.

Notes

Acknowledgments. Members of IDSA Sepsis Task Force include Andre C. Kalil, MD, University of Nebraska Medical Center, Omaha, Nebraska; David N. Gilbert, MD, Providence Portland Medical Center, Portland, Oregon; Dean L. Winslow, MD, Stanford University Medical Center, Palo Alto, California; Henry Masur, MD, NiH Clinical Center, Bethesda, Maryland; Michael Klompas, MD, Harvard Medical School, Boston, Massachusetts. Dr. Masur represented IDSA on the writing committee for the Surviving Sepsis Campaign Guidelines section on the diagnosis and therapy of microbial infections.

Financial support. This research was supported in part by the Intramural Research Program of the National Institutes of Health Clinical Center.

Potential conflict of interest. No author has a conflict of interest related to this submission. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* **2017**; 45:486–552.
- Klein Klouwenberg PM, Cremer OL, van Vught LA, et al. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. *Crit Care* **2015**; 19:319.
- Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* **1992**; 101:1644–55.
- Levy MM, Fink MP, Marshall JC. SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* **2003**; 31:1250–6.
- Singer M, Deutschman CS, Seymour CW, et al. Septic shock (Sepsis-3). *JAMA* **2016**; 315:801–10.
- Sterling SA, Puskari MA, Glass AE, Guirgis F, Jones AE. The impact of the sepsis-3 septic shock definition on previously defined septic shock patients. *Crit Care Med* **2017**; 45:1436–42.
- SEP-1: Early Management Bundle, Severe Sepsis/Septic Shock. Available at: https://www.mhnet.com/mhimages/Sepsis_FactSheet.pdf. Accessed 29 August 2017.
- National Quality Forum. NQF #0500 Severe sepsis and septic shock: management bundle. Available at <http://www.qualityforum.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=71548>. Accessed 28 August 2017.
- Institute for Healthcare Improvement. Severe sepsis bundles. Available at <http://www.ihp.org/resources/Pages/Tools/SevereSepsisBundles.aspx>. Accessed 28 August 2017.
- Kalil AC, Johnson DW, Lisco SJ, Sun J. Early goal-directed therapy for sepsis: a novel solution for discordant survival outcomes in clinical trials. *Crit Care Med* **2017**; 45:607–14.
- Bloos F, Thomas-Rüddel D, Rüddel H, et al.; MEDUSA Study Group. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. *Crit Care* **2014**; 18:R42.
- Garber AM. Evidence-based guidelines as a foundation for performance incentives. *Health Aff* **2005**; 24:174–9.
- Dellinger RP, Schorr CA, Levy MM. A users' guide to the 2016 surviving sepsis guidelines. *Crit Care Med* **2017**; 45:381–5.
- Kumar A, Roberts D, Wood KE, 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**; 34:1589–96.
- Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med* **2017**; 376:2235–44.
- Ferrer R, Martin-Loeches I, Phillips G, 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**; 42:1749–55.
- Sterling SA, Miller WR, Pryor J, Puskari MA, Jones AE. The impact of timing of antibiotics on outcomes in severe sepsis and septic shock: a systematic review and meta-analysis. *Crit Care Med* **2015**; 43:1907–15.
- Singer M. Antibiotics for sepsis—does each hour really count? or is it incestuous amplification? *Am J Respir Crit Care Med* **2017**. doi: 10.1164/rccm.201703-0621ED.
- Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. *Am J Respir Crit Care Med* **2017**. doi: 10.1164/rccm.201609-1848OC.
- IDSA guidelines for the diagnosis and management of intravascular catheter-related bloodstream infection. *Clin Infect Dis* **2009**; 49:1770–1.
- Klompas M. Monotherapy is adequate for septic shock due to gram-negative organisms. *Crit Care Med* **2017**; 45:1930–2.
- Kalil AC. Antibiotic combination therapy for patients with gram-negative septic shock. *Crit Care Med* **2017**; 45:1933–1936.
- Kumar A, Safdar N, Kethireddy S, Chateau D. A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-analytic/meta-regression study. *Crit Care Med* **2010**; 38:1651–64.
- Kumar A, Zarychanski R, Light B, et al.; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. *Crit Care Med* **2010**; 38:1773–85.
- Al-Hasan MN, Wilson JW, Lahr BD, et al. Beta-lactam and fluoroquinolone combination antibiotic therapy for bacteremia caused by gram-negative bacilli. *Antimicrob Agents Chemother* **2009**; 53:1386–94.
- Delannoy PY, Boussekey N, Devos P, et al. Impact of combination therapy with aminoglycosides on the outcome of ICU-acquired bacteraemias. *Eur J Clin Microbiol Infect Dis* **2012**; 31:2293–9.
- Diaz-Martin A, Martinez-Gonzalez ML, Ferrer R, et al.; Edusepsis Study Group. Antibiotic prescription patterns in the empiric therapy of severe sepsis: combination of antimicrobials with different mechanisms of action reduces mortality. *Crit Care* **2012**; 16:R223.
- Martin-Loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med* **2010**; 36:612–20.
- Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev* **2014**:CD003344.
- Kumar A, Zarychanski R, Light B, et al.; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. *Crit Care Med* **2010**; 38:1773–85.
- Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis* **2004**; 4:519–27.
- Hu Y, Li L, Li W, et al. Combination antibiotic therapy versus monotherapy for *Pseudomonas aeruginosa* bacteraemia: a meta-analysis of retrospective and prospective studies. *Int J Antimicrob Agents* **2013**; 42:492–6.
- Brunkhorst FM, Oppert M, Marx G, et al.; German Study Group Competence Network Sepsis (SepNet). Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial. *JAMA* **2012**; 307:2390–9.
- Baddour LM, Yu VL, Klugman KP, et al.; International Pneumococcal Study Group. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am J Respir Crit Care Med* **2004**; 170:440–4.
- Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* **2016**; 63:e61–e111.
- de Jong E, van Oers JA, Beishuizen A, 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**; 16:819–27.
- Bouadma L, Luyt CE, Tubach F, et al.; PRORATA trial group. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* **2010**; 375:463–74.
- Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med* **2015**; 372:1996–2005.
- Uranga A, España PP, Bilbao A, et al. Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. *JAMA Intern Med* **2016**; 176:1257–65.
- el Moussaoui R, de Borgie CA, van den Broek P, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ* **2006**; 332:1355.
- Dunbar LM, Wunderink RG, Habib MP, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin Infect Dis* **2003**; 37:752–60.
- Chastre J, Wolff M, Fagon JY, et al.; PneumA Trial Group. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* **2003**; 290:2588–98.
- Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit: a proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* **2000**; 162:505–11.
- Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection—7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* **2013**; 68:2183–91.