AMERICAN THORACIC SOCIETY DOCUMENTS

Antibiotic Stewardship in the Intensive Care Unit

An Official American Thoracic Society Workshop Report in Collaboration with the AACN, CHEST, CDC, and SCCM

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This official workshop report of the American Thoracic Society was approved by the American Thoracic Society February 2020, and by the American Association of Critical-Care Nurses, the American College of Chest Physicians, the Centers for Disease Control and Prevention, and the Society of Critical Care Medicine January 2020

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Abstract

Intensive care units (ICUs) are an appropriate focus of antibiotic stewardship program efforts because a large proportion of any hospital's use of parenteral antibiotics, especially broad-spectrum, occurs in the ICU. Given the importance of antibiotic stewardship for critically ill patients and the importance of critical care practitioners as the front line for antibiotic stewardship, a workshop was convened to specifically address barriers to antibiotic stewardship in the ICU and discuss tactics to overcome these. The working definition of antibiotic stewardship is "the right drug at the right time and the right dose for the right bug for the right duration." A major emphasis was that antibiotic stewardship should be a core competency of critical care clinicians. Fear of pathogens that are not covered by empirical antibiotics is a major driver of excessively broad-spectrum therapy in critically ill patients. Better diagnostics and outcome data can address this fear and expand efforts to narrow or shorten therapy. Greater awareness of the substantial adverse effects of antibiotics should be emphasized and is an important counterargument to broad-spectrum therapy in individual low-risk patients. Optimal antibiotic stewardship should not focus solely on reducing antibiotic use or ensuring compliance with guidelines. Instead, it should enhance care both for individual patients (by improving and individualizing their choice of antibiotic) and for the ICU population as a whole. Opportunities for antibiotic stewardship in common ICU infections, including community- and hospital-acquired pneumonia and sepsis, are discussed. Intensivists can partner with antibiotic stewardship programs to address barriers and improve patient care.

Keywords: antibiotic stewardship; antibiotic resistance; pneumonia; sepsis

This workshop report was sponsored by the Acute Pneumonia Working Group of the American Thoracic Society Assembly on Pulmonary Infections and Tuberculosis.

This document was funded by the American Thoracic Society with funding for individual representatives to the committee meeting by the Centers for Disease Control and Prevention, American Association of Critical-Care Nurses, American College of Chest Physicians, and the Society of Critical Care Medicine. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Department of Veterans Affairs.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Ann Am Thorac Soc Vol 17, No 5, pp 531–540, May 2020

DOI: 10.1513/AnnalsATS.202003-188ST
Internet address: www.atsjournals.org

Contents

Introduction

Increasing rates and types of antibiotic resistance and a limited antibiotic pipeline, particularly for gram-negative pathogens, have led to an international crisis. In the United States, a Presidential Executive Order directed government research emphasis and resources to address this issue (1). A major component of the action plan for the Combating Antibiotic-Resistant Bacteria initiative is the enhancement of antibiotic stewardship programs (ASPs) to preserve the activity of current and future antibiotics (1).

Intensive care units (ICUs) are an appropriate focus of ASP efforts because a large proportion of any hospital's use of parenteral antibiotics, especially broad-spectrum, occurs in the ICU (2). The ICU is also the locus of many patients with life-threatening infections due to multidrug-resistant (MDR) bacteria (3). However, despite general support for ASPs by intensivists (4–6), the philosophical approaches and priorities of critical care practitioners and ASPs can differ (7). Although all involved desire the best patient outcomes, the potentially competing goals of adequate empirical antimicrobial therapy and antibiotic stewardship sometimes create tension. If stewardship efforts are to succeed, this conflict must be addressed. The goal of most critical care practitioners is rapid provision of the appropriate initial therapy. ASPs must work with ICU clinicians to ensure the rapid delivery of effective antibiotics to critically ill infected patients, and intensivists must work with ASPs on efforts to tailor or stop antibiotics when indicated. Regardless of which approach is used, antibiotic stewardship efforts are likely to be frustrated without a substantial buy-in by the clinicians who are primarily caring for the patients (8, 9).

Notable antibiotic stewardship efforts have already been established at a national and international levels, including guidelines for implementing ASPs (10). The current guidelines were principally developed for ASPs and do not directly address initiatives for clinicians who are primarily responsible for patient care, particularly in the ICU.

Given the importance of antibiotic stewardship for critically ill patients and the importance of critical care practitioners as the front line for antibiotic stewardship (6, 11), a workshop was convened to specifically address barriers to antibiotic stewardship in the ICU and discuss tactics to overcome them. This report represents a synthesis of the major themes that emerged from discussions among the participants.

Methods

The Acute Pneumonia Working Group of the Pulmonary Infections and Tuberculosis Assembly of the American Thoracic Society (ATS) originally initiated a proposal for a Workshop on Antimicrobial Stewardship in the ICU. The ATS convened the workshop and invited other members of the Critical Care Societies Collaborative and the Centers for Disease Control and Prevention to participate, and each sent representatives. Potential conflicts of interest were disclosed and managed in accordance with the policies and procedures of the ATS. A multidisciplinary group of 26 Pulmonary, Critical Care, Surgery, Infectious Diseases, Nursing, and Critical Care Pharmacist practitioners participated in the workshop, which was held May 13, 2016. The primary focus was to identify issues and recognize opportunities for antibiotic stewardship targeted toward individual patients by ICU clinicians at the bedside. Further details regarding the workshop are included in the online supplement.

General

Several major themes emerged from the workshop (Table 1); this report focuses on these general principles and offers some illustrative examples.

As endorsed by workshop participants, the working definition of antibiotic stewardship is "the right drug at the right time with the right dose for the right bug for the right duration." Implicit in this definition is that stewardship involves substantially more than antibiotic de-escalation or discontinuation. Throughout the discussions, clinical outcomes remained the primary concern, with the clear recognition that antibiotics prescribed for one patient may have deleterious effects on other patients.

This working definition of antibiotic stewardship did not include the words "at the right cost." A heavy emphasis on acquisition costs and access restriction in prior ASP initiatives had such a negative connotation that alternative terminology, such as "antibiotic optimization," was considered. However, the participants chose to continue using this more standard terminology while emphasizing the breadth of issues involved.

Table 1. Major themes in antibiotic stewardship in the intensive care unit

- Critical care practitioners are important causes of and potential solutions to the crisis of antibiotic resistance.
- Antibiotic stewardship should be considered a core competency of critical care practitioners.
- Antibiotic stewardship must address the fear of inadequate empirical treatment in the critically ill to be effective.
- The adverse effect of excessive antibiotic treatment on the individual patient needs greater emphasis.
- Antibiotic stewardship programs must ensure that improving overall antibiotic use, not simply reducing antibiotic costs or increasing de-escalation, is the primary focus.
- The hope of rapid diagnostics is currently largely unfulfilled.
- A shift in emphasis to an individualized approach to antibiotic therapy is needed.

Antibiotic Stewardship Should Be a Core Competency of Critical Care Practitioners

The first theme that emerged is that antibiotic stewardship should be a core competency of critical care practitioners. Compared with other hospital clinicians, critical care practitioners disproportionately confront antibiotic resistance. The point prevalence of antibiotic use in ICUs is 70%, with only 45% of patients having culture- or imaging-confirmed infection (12). Although the local incidence of MDR pathogens varies among institutions, they can cause up to 30% of cases of gram-negative bacteremia (13, 14). Patients who fail inpatient antibiotic therapy are more likely to have resistant pathogens and often require transfer to the ICU. Broad-spectrum antibiotic therapy is often prescribed empirically for patients with community-acquired pneumonia (CAP) who have been transferred to the ICU, even though there are multiple other reasons for the apparent treatment failure. Even short courses of empirical broad-spectrum antibiotics may increase the risk of further antibiotic resistance, leading to a vicious cycle of escalating antibiotic resistance. Therefore, antibiotics prescribed by critical care practitioners may contribute substantially to antibiotic resistance.

Critical care practitioners are also a major part of the solution. Their expertise, logistics, and existing multiprofessional teamwork, along with the limited ASP staffing and time, place critical care practitioners at the front line of decisions regarding antibiotics in the ICU. The rapidly changing condition of many critically ill patients requires the same type of on-site, dynamic team decision-making for antibiotic treatment as is done routinely by critical care practitioners for issues involving hemodynamics, ventilator use, and other ICU problems (15). Empowering staff to speak up and ask about antibiotic therapy is imperative. Critical care pharmacists are well positioned to ensure rapid delivery of antibiotics for an individual patient. In many cases, antibiotic use begins outside the ICU, before patients are transferred from other inpatient units, referring hospitals, or the emergency department. Antibiotic optimization can be accomplished most efficiently immediately upon transfer, with subsequent refinement by an ASP.

Critical care practitioners may be optimally situated to educate trainees regarding antibiotic stewardship. Decisions about antibiotics are frequently made by residents and fellows who are taught to cover broadly and often are not empowered to stop the use of unnecessary or inappropriately broad-spectrum antibiotics. Innovative dosing based on optimization of pharmacokinetics/pharmacodynamics, such as continuous or prolonged β-lactam infusions (16), is most pertinent to the critically ill, and modifying the initial antibiotic orders in accordance with such a strategy provides an opportunity to teach important pharmacokinetic/pharmacodynamic principles. Making the direct instruction of trainees regarding antibiotics and formal review of antibiotic choices on ICU rounds an integral component of clinical care benefits not only the individual patient but all subsequent patients (17).

Importantly, integration of critical care practitioners with ASPs has important implications for ASP implementation in the critical care environment. Audit and feedback to the primary service, an important ASP intervention (10), can be performed in different ways. Much ASP feedback, particularly for trainees, is for individual cases rather than for overall patterns. For such feedback to be effective, comprehensive data need to reach individual prescribers and units, not just ASPs. Feedback that benchmarks appropriate antibiotic use relative to peers may motivate proper use, in a manner similar to tactics used previously for surgical site infections. Importantly, no disincentive for overuse of antibiotics currently applies directly to critical care practitioners, representing another opportunity for collaboration with ASPs. A multiprofessional approach to antibiotic stewardship is appealing because it would provide multiple opportunities to optimize the use of antibiotics (18).

The practical implication of this workshop conclusion is that critical care training programs need to develop a curriculum to incorporate this educational agenda. In addition, practicing clinicians need to participate in continuing medical education on critical care antibiotic stewardship.

Fear Drives Much Excess Antibiotic Use

Fear, rather than a knowledge deficit, is the greatest barrier to avoiding excessive use of antibiotics (8). Shorter times to initiation of the appropriate antibiotic therapy are consistently associated with better outcomes for infections in the critically ill (19). Fear of missing the causative pathogen, with resultant adverse clinical outcomes, is a major theme. Because critical care practitioners often manage undifferentiated critically ill patients whose infectious etiology, antibiotic susceptibility, and even site of infection may be unknown, empirical treatment that is much broader than what would ultimately be required once these factors are known is usually necessary (20). However, therapy is narrowed for only 30–40% of patients on empirical broad-spectrum antibiotics when evidence of resistant pathogens is lacking (21, 22).

Fear of missing a pathogen also drives broadening antibiotic coverage for infections in which deterioration or even a lack of improvement early in the course of treatment is expected. For example, new-onset hypotension after the first dose of a β-lactam antibiotic often results in escalation from usual CAP treatment to broad-spectrum antibiotics, despite a low likelihood of missing pathogens (23).

This fear often leads to friction and a breakdown in trust with ASPs (24). For intensivists, curing the patient is paramount, whereas costs or antibiotic use metrics are perceived by many to be ASP priorities. This tension reflects the inherent conflict between patient-level and societal priorities (25). The conflict can be complicated further if documentation of ASP antibiotic directives is not placed in the patient's medical record (20). Unless this fear of missing pathogens is acknowledged and addressed, efforts to improve antibiotic use for critically ill patients will be blunted. More and higher-quality studies are needed to demonstrate the safety of narrower/less antibiotic therapy (26, 27). Importantly, these studies must assess the safety of narrowing or stopping antibiotic therapy in culture-negative patients, who may experience adverse outcomes equivalent to those of culture-positive patients (28).

Greater Emphasis on the Adverse Effects of Antibiotics Is Needed

A corollary to the fear of missing causative pathogens is the general impression that antibiotics "can't hurt." This belief is particularly true for the critically ill patient, where the false assumptions of "spiraling empiricism"—sicker patients require more antibiotics, sicker patients require broader-spectrum antibiotics—are commonly invoked (29). Stewardship efforts must emphasize the evidence regarding the

adverse effects of excessive antibiotics to correct this knowledge deficit (30, 31).

An individual patient's risk of adverse events from excessive antibiotic therapy counterbalances the fear of missing pathogens more effectively than the societal argument. A predisposition to subsequent nosocomial infections, including *Clostridioides difficile* infection, is recognized, but the frequency is underappreciated (32–34). Unnecessary or excessively broad-spectrum antibiotics even predispose to subsequent sepsis (35). Although the substantial nephrotoxicity associated with the ubiquitous empirical combination of vancomycin and piperacillin/tazobactam is increasingly recognized (36), the risk of many other combinations is underappreciated. Rapid de-escalation appears to ameliorate this risk (37).

Optimizing ASP Implementation

ASPs often focus on compliance with antibiotic treatment guidelines promulgated by specialty societies. However, rigid adherence to these guidelines may not improve antibiotic stewardship (38). The primary goal of guidelines is to decrease suboptimal care, and this has been achieved in many instances (39–41). However, decreasing the variability of antibiotic treatment by strictly following guidelines may actually prevent superior care in some cases. For example, monotherapy may be more appropriate for a patient with CAP and many gram-positive diplococci in a high-quality sputum specimen than the guideline-recommended treatment (β-lactam/macrolide combination). Optimal antibiotic stewardship would shift the range of treatments out of suboptimal treatment but retain the superior care, improving care overall.

ASPs must also ensure that improving overall antibiotic use, not simply reducing the cost of antibiotics, is the primary focus. Previously, some ASPs heavily emphasized cost in response to pressure from hospital leadership to save money on antibiotics. Likewise, ASPs must be continually vigilant to ensure that stewardship efforts, especially antibiotic restrictions, do not lead to unanticipated increases in the use of unrestricted agents and subsequent resistance to them (42).

Finally, ASPs must take additional steps to monitor the safety of stewardship interventions, especially for critically ill patients. The limited available data suggest that stewardship interventions are generally safe (43); however, safety is not mentioned in many ASP studies (24, 44). Likewise, most stewardship studies do not specifically attempt to address concerns that providers might have about implementing an intervention. During the design of stewardship interventions, ASPs should partner with providers, especially intensivists, to determine which safety measures should be tracked along with reduced antibiotic use and to discuss potential concerns about implementation.

The Hope of Rapid Diagnostics Is Currently Unfulfilled

Narrowing or discontinuation of antibiotics is much more likely to occur when the appropriate diagnostics are obtained at the onset of infection, especially before initiation of antibiotic treatment (21). The benefits of rapid diagnostic tests for clinical care and their ability to decrease excessive antibiotic use are highly anticipated. However, this optimism requires extensive clinical validation, especially with regard to de-escalation (45). The availability of rapid diagnostics may change management strategies if turnaround times and operating characteristics are sufficient to affect clinical decisions. Validation of a diagnostic test must be sufficient to overcome clinicians' fear of missing pathogens or antibiotic resistance if antibiotic management is based on the result (46–48). A rapid test sensitivity equivalent to culture for pathogen detection is easier to achieve than the molecular diagnosis equivalent of culture-based antibiotic susceptibility. The lowest-hanging fruit may be *Staphylococcus aureus*, where a single mutation predicts methicillin resistance (26, 49). Determining antibiotic susceptibility by a rapid test for *Pseudomonas aeruginosa* or other MDR pathogens is much more complex (50).

Rapid diagnostics other than those used for positive blood cultures are a crucial need. Bacteremia rates are low even among critically ill patients with well-established sites of infection. Rapid diagnostics for pathogen detection directly from blood samples (without a culture step) and specimens from other sources, especially respiratory sources, are critical for antibiotic stewardship in the ICU. Quantitation becomes a major challenge in samples where microbial colonization is common, such as tracheal aspirates and catheterized urine. Lower cost effectiveness compared with empirical therapy and culture-based diagnosis may be a major barrier to the routine use of rapid diagnostics. Clearly, neither antibiotic stewardship nor cost effectiveness will improve if clinicians ignore the results of rapid diagnostics and continue to use empirical antibiotics (45). Critical care practitioners are in a great position to act on the results of rapid diagnostic tests in a timely manner, and should be included in the implementation plan.

Biomarkers can assist antibiotic stewardship as well. Most currently available biomarkers target the host inflammatory response and therefore are notoriously less accurate for establishing a diagnosis in critically ill patients with multiple other causes of inflammation or impaired immune function. However, a consistent pattern of safely shortening the duration of antibiotic treatments based on a marked improvement or normalization of biomarkers, such as procalcitonin and C-reactive protein, has been demonstrated in critically ill patients with a variety of infections (51–54).

A Shift in Emphasis to Individualization Is Needed

A recurring theme is that individualization—to a specific hospital, unit, or even patient—optimizes the prescribing of antibiotics. ASPs tend to look to professional society guidelines for recommendations regarding antibiotic therapy for specific infections. However, each major guideline for hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP), CAP, and sepsis recommends local adaptation of guideline-recommended therapy (55–58). Guideline recommendations tend to reflect the type of hospital where most of the guideline authors practice, with a consequent bias toward large academic centers. However, the strategies used by ASPs in large academic centers likely differ from the best approaches for community-based, nonteaching, nonacademic hospitals. Only recently have guidelines offered assistance to determine when primary recommendations might be altered, such as when empirical methicillin-resistant *S. aureus* (MRSA) coverage is needed for HAP/VAP (55).

Guidelines emphasize the need for ICU-specific antibiograms, but many hospitals are unable to provide these reports.

In addition, antibiograms tend to emphasize "reliable" cultures, which often excludes respiratory cultures. The HAP/VAP spectrum of etiology and antibiotic susceptibility patterns differs substantially from a spectrum based solely on bacteremia or urinary tract infection, depending on the reliability of the respiratory culture. In this setting, the clinical experience of critical care practitioners may be more accurate than hospital-wide antibiograms. Attempts to limit antibiotic access or de-escalate before obtaining positive cultures based on hospital-wide antibiograms and guidelines may therefore meet with resistance. Tools for ICUs to assess their individual need for diagnostic/treatment algorithms that differ from those recommended by a professional society are sorely needed.

Individualization to the patient-specific level is ideal. Although individualization will be challenging until rapid, accurate diagnostics are routinely available, prudent steps can be taken. For example, avoidance of repeated courses of the same antibiotic regimen is prudent, even if the agent is guideline recommended (59). Altered volumes of distribution and fluctuating renal function can make standard dosing regimens inadequate for acutely ill patients. Dosing of antibiotics also needs to be individualized, especially for patients with augmented renal clearance (58, 60). Nonstandard antibiotic dosing and therapeutic drug monitoring, when available, may be necessary.

Critical Care Specific Opportunities

To address these challenges, ASPs can collaborate with intensivists to develop local treatment guidelines that might be based on national guidelines but are tailored to local data and expertise. Workshop participants also discussed opportunities to improve antibiotic stewardship for three specific infections pertinent to critical care practitioners (CAP, HAP/VAP, and sepsis/septic shock), which were chosen *a priori* based on existing society guidelines, frequency of occurrence in the ICU, and associated morbidity/mortality.

Community-acquired Pneumonia

One of the greatest current opportunities for antibiotic stewardship is the elimination of the healthcare-associated pneumonia (HCAP) designation for some patients with CAP (61). Although they are consistently more common in patients admitted to the ICU, the incidence of pathogens that are resistant to usual CAP antibiotics is very low (62–65). The HCAP paradigm resulted in significant overtreatment of CAP, with evidence of actual adverse consequences in retrospective cohorts (62, 66). The term "HCAP" is now eliminated from pneumonia guidelines, but the efficacy and safety of management based on risk factors for specific pathogens that are resistant to the usual CAP antibiotics will require future validation.

The greater consensus regarding empirical antibiotic treatment for CAP than is the case for most other ICU infections allows for greater implementation of several antibiotic stewardship principals for this infection (40). Adherence can be improved by making the use of suggested antibiotics via guideline-compliant electronic order sets the easiest/default strategy (67). Automated prompts and decision support from electronic health records may further reinforce the appropriate use of antibiotics in CAP (68).

Audit and feedback benchmarking appropriate antibiotic use relative to peers may be helpful and motivate proper use. Previous HCAP guidelines changed prescribing patterns and payments for CAP (69, 70). Currently, there is no disincentive for overtreatment of CAP. Disincentives promulgated by the Centers for Medicare and Medicaid Services or other groups may provide one way to move past the influence of previous HCAP guidelines regarding prescriptions for CAP.

In contrast to HAP/VAP, regional antibiograms for CAP are probably more important than local data. The risk of antibiotic-resistant *S. pneumoniae* is significantly lower as the result of pediatric (and now adult) protein-conjugate pneumococcal vaccines (71). Conversely, the prevalence of extended-spectrum β-lactamases in Enterobacteriaceae causing CAP is increasing, as is the prevalence of community-acquired MRSA (61). However, the incidence of each still remains very low (63, 64, 72, 73). Specific risk factors for community-acquired MRSA can both identify patients who likely need empirical coverage and minimize the use of vancomycin or linezolid (74, 75). A simple need for ICU admission is not a sufficient risk factor for universal anti-MRSA coverage (76).

Two major issues remain for antibiotic stewardship of CAP: severe CAP (SCAP) and possible viral SCAP. Whereas the frequency of specific etiologies in SCAP varies from noncritically ill patients (more *S. aureus*, *Legionella spp.*), the association between severity at presentation and the need for broad-spectrum antibiotic therapy is weak (72, 77). Because patients with SCAP are routinely excluded from clinical trials of new antibiotics, most antibiotic recommendations rely on etiologies identified in observational cohorts. When patients with CAP deteriorate and require delayed ICU transfer, differentiating between missed pathogens and an exaggerated host response despite appropriate antibiotic therapy is difficult for clinicians.

Molecular tests detect viruses in a high proportion of CAP cases, including in critically ill patients (63), and studies have shown that assessment of procalcitonin levels may allow safe avoidance of antibiotics in outpatients and hospitalized patients with probable viral pneumonia (52). However, patients with SCAP were specifically excluded from these studies, and procalcitonin may correlate more highly with severity than with etiology in these patients (78).

Hospital-acquired/Ventilator Associated Pneumonia

Treatment guidelines for HAP/VAP are increasingly difficult to write, and the applicability to individual ICUs is correspondingly compromised (55, 57). The benefit of compliance with guidelines is less well demonstrated for HAP/VAP than for CAP (38, 79, 80). Increased frequency and new patterns of antibiotic resistance occur faster than completion of novel treatment studies. Therefore, treatment studies available for evidence-based guideline meta-analyses are often outdated or inconclusive at the time of guideline development (81). Most antibiotic treatment studies are pharmaceutical-sponsored registration trials, from which many critically ill patients with HAP/VAP (e.g., those with compromised immune systems or liver failure) are specifically excluded. Therefore, algorithms based on local culture patterns or antibiotic susceptibilities are more meaningful than algorithms based on national data. Review of an individual's recent antibiotic therapy is crucial to avoid resuming a drug for which prior treatment

pressure is likely to select for resistant pathogens.

The greatest opportunity for antibiotic stewardship may be stopping antibiotics for culture-negative HAP/VAP (34, 82, 83). This approach is critically dependent on obtaining accurate early cultures, which is much more feasible in intubated patients. In many of these cases, an alternative cause of symptoms/signs of pneumonia can be found, such as a nonpulmonary infection that requires different-spectrum antibiotics, device removal, or drainage procedures for optimal management (84, 85). In circumstances where pneumonia is still suspected clinically, although it does not necessarily rule out pneumonia, a negative respiratory culture from an intubated patient has a high negative predictive power for MDR pathogens such as *P. aeruginosa*, *Acinetobacter* spp., and MRSA, at least compared with nonculture techniques (26, 86). Antibiotic therapy can be correspondingly de-escalated, potentially decreasing the emergence of MDR pathogens (87).

The duration of the appropriate therapy is another important area for HAP/VAP antibiotic stewardship (24, 27). Previously, the duration of antibiotic therapy was arbitrary and based on the calendar rather than on evidence. Recent studies demonstrated that ⩽8 days of treatment is adequate for the majority of patients (33, 51). Major guidelines recommend a 7- to 8-day course as the standard, with caveats for populations that were not included in the original studies, such as immunocompromised patients (33, 55, 57). It is feared that shorter courses may lead to inadequate control of infection and recurrence when the antibiotics are stopped, particularly in the case of VAP due to *P. aeruginosa* and other MDR pathogens. Whether a longer course of the same antibiotic regimen improves outcomes for these pathogens remains controversial, with high recurrence rates and mortality thus far appearing to be independent of the duration of antibiotics (27, 33, 88).

An additional opportunity that is most pertinent to HAP/VAP but is also applicable to antibiotic stewardship of other infections is appropriate evaluation or desensitization of patients with a poorly documented β-lactam "allergy." The use of non–β-lactam regimens in hospitalized patients is associated with worse outcomes (89). Conversely, skin testing and desensitization protocols are low risk (90), even in the critically ill.

Sepsis/Septic Shock

Early administration of appropriate antibiotics consistently improves survival of patients with CAP, HAP/VAP, and sepsis in general, while also decreasing associated organ failure, including progression to septic shock, acute respiratory distress syndrome, and acute kidney injury (19, 91–95). In retrospective studies, the effect of time to first appropriate antibiotic in patients with hypotension is measured in hours (96, 97). Workshop participants therefore expressed great concern regarding the ASP strategy of requiring preauthorization of certain antibiotics for critically ill patients (10), particularly hypotensive ones.

Because of the heterogeneity of patients with sepsis or septic shock, a single recommended regimen for "sepsis" will likely result in inappropriately broad treatment for a large proportion of patients and occasionally a too-narrow spectrum. For example, a default "sepsis" regimen of piperacillin/tazobactam and vancomycin is inappropriate and potentially dangerous for patients with CAP simply because they are hypotensive (36, 62, 66); pan-susceptible *S. pneumoniae* is still the most likely pathogen and is optimally treated with the standard ceftriaxone and macrolide. Antibiotic protocols that are appropriate for the suspected source and patient profile are likely to be equally effective and exert less antibiotic pressure. The development of such local guidelines presents an excellent opportunity for ASPs to partner with intensivists.

Antibiotic stewardship for the critically ill surgical patient introduces another major consideration (98). The adequacy of source control by the surgical procedure or drainage has major implications for the duration of antibiotic therapy. Communication with the operating surgeon/proceduralist regarding the initial adequacy of source control and ongoing assessment is critical for antibiotic management. Appropriate timing and duration of perioperative antibiotic prophylaxis and therapy also impact the risk of subsequent surgical site infections.

The current focus on improving outcomes in patients with sepsis presents an important opportunity for collaboration between ASPs and intensivists. Ideally, hospitals should take a multiprofessional approach toward determining the optimal antibiotics for various types of patients presenting with sepsis, and ensuring that antibiotics are delivered promptly. After antibiotic therapy is initiated, ASPs and intensivists can work together to optimize the therapy (e.g., by broadening, narrowing, or stopping it). Stopping antibiotics is an important consideration because data suggest that up to 40% of patients with suspected sepsis may not have an infection (99).

Summary

Antibiotic stewardship should be a core competency of critical care practitioners, and training programs and continuing medical education are needed to address and assess this skill. The idea of incorporating intensivists into a multiprofessional approach to antibiotic stewardship is appealing, and would provide opportunities to optimize ICU antibiotic management. Future research should address the fear of missed pathogens and MDR organisms through outcome studies and clinical trials, to avoid hindering antibiotic stewardship for critically ill patients. ■

This official workshop report was prepared by an *ad hoc* committee with representatives from the ATS, AACN, CHEST, CDC, and SCCM.

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References

1 The President's Council of Advisors on Science and Technology. Report to the President on combating antibiotic resistance. September 2014 [accessed 2020 Apr 12]. Available from: https://www.cdc.gov/drugresistance/pdf/report-to-the-president-on-combating-antibiotic-resistance.pdf.

2 Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, *et al*.; EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009;302:2323–2329.

3 Tabah A, Koulenti D, Laupland K, Misset B, Valles J, Bruzzi de Carvalho F, *et al*. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. *Intensive Care Med* 2012;38:1930–1945.

4 Steinberg M, Dresser LD, Daneman N, Smith OM, Matte A, Marinoff N, *et al*. A national survey of critical care physicians' knowledge, attitudes, and perceptions of antimicrobial stewardship programs. *J Intensive Care Med* 2016;31:61–65.

5 Kollef MH, Micek ST. Antimicrobial stewardship programs: mandatory for all ICUs. *Crit Care* 2012;16:179.

6 Decker B, Masur H. Bad bugs, no drugs: are we part of the problem, or leaders in developing solutions? *Crit Care Med* 2015;43:1153–1155.

7 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.

8 Broom J, Broom A. Guideline relevance, diagnostic uncertainty, fear and hierarchy: intersecting barriers to antibiotic optimization in respiratory infections. *Respirology* 2018;23:733–734.

9 Charani E, Castro-Sanchez E, Sevdalis N, Kyratsis Y, Drumright L, Shah N, *et al*. Understanding the determinants of antimicrobial prescribing within hospitals: the role of "prescribing etiquette". *Clin Infect Dis* 2013;57:188–196.

10 Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). *Infect Control Hosp Epidemiol* 2012;33:322–327.

11 Kadri SS. Recognizing the unique role of critical care providers in confronting antimicrobial resistance. *Am J Respir Crit Care Med* 2018;198:560–562.

12 Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, *et al*.; EPIC International Advisory Committee. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) study. *JAMA* 1995;274:639–644.

13 Orsini J, Mainardi C, Muzylo E, Karki N, Cohen N, Sakoulas G. Microbiological profile of organisms causing bloodstream infection in critically ill patients. *J Clin Med Res* 2012;4:371–377.

14 Adrie C, Garrouste-Orgeas M, Ibn Essaied W, Schwebel C, Darmon M, Mourvillier B, *et al*.; OUTCOMEREA Study Group*. Attributable

mortality of ICU-acquired bloodstream infections: impact of the source, causative micro-organism, resistance profile and antimicrobial therapy. *J Infect* 2017;74:131–141.
15 McKenzie MS, Auriemma CL, Olenik J, Cooney E, Gabler NB, Halpern SD. An observational study of decision making by medical intensivists. *Crit Care Med* 2015;43:1660–1668.
16 Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G, Falagas ME. Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. *Lancet Infect Dis* 2018;18:108–120.
17 Weiss CH, Moazed F, McEvoy CA, Singer BD, Szleifer I, Amaral LA, *et al*. Prompting physicians to address a daily checklist and process of care and clinical outcomes: a single-site study. *Am J Respir Crit Care Med* 2011;184:680–686.
18 Fleming D, Ali KF, Matelski J, D'Sa R, Powis J. When antimicrobial stewardship isn't watching: the educational impact of critical care prospective audit and feedback. *Open Forum Infect Dis* 2016;3:ofw115.
19 Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, *et al*.; Cooperative Antimicrobial Therapy of Septic Shock Database Research Group. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest* 2009;136:1237–1248.
20 Broom J, Broom A, Plage S, Adams K, Post JJ. Barriers to uptake of antimicrobial advice in a UK hospital: a qualitative study. *J Hosp Infect* 2016;93:418–422.
21 Braykov NP, Morgan DJ, Schweizer ML, Uslan DZ, Kelesidis T, Weisenberg SA, *et al*. Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study. *Lancet Infect Dis* 2014;14:1220–1227.
22 Bergmans DC, Bonten MJ, Gaillard CA, van Tiel FH, van der Geest S, de Leeuw PW, *et al*. Indications for antibiotic use in ICU patients: a one-year prospective surveillance. *J Antimicrob Chemother* 1997;39: 527–535.
23 Micek ST, Lang A, Fuller BM, Hampton NB, Kollef MH. Clinical implications for patients treated inappropriately for community-acquired pneumonia in the emergency department. *BMC Infect Dis* 2014;14:61.
24 Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017;2:CD003543.
25 Dyar OJ, Obua C, Chandy S, Xiao Y, Stålsby Lundborg C, Pulcini C. Using antibiotics responsibly: are we there yet? *Future Microbiol* 2016;11:1057–1071.
26 Paonessa JR, Shah RD, Pickens CI, Lizza BD, Donnelly HK, Malczynski M, *et al*. Rapid detection of methicillin-resistant *Staphylococcus aureus* in BAL: a pilot randomized controlled trial. *Chest* 2019;155: 999–1007.
27 Micek ST, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest* 2004;125:1791–1799.
28 Bekaert M, Timsit JF, Vansteelandt S, Depuydt P, Vésin A, Garrouste-Orgeas M, *et al*.; Outcomerea Study Group. Attributable mortality of ventilator-associated pneumonia: a reappraisal using causal analysis. *Am J Respir Crit Care Med* 2011;184:1133–1139.
29 Kim JH, Gallis HA. Observations on spiraling empiricism: its causes, allure, and perils, with particular reference to antibiotic therapy. *Am J Med* 1989;87:201–206.
30 Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Intern Med* 2017;177:1308–1315.
31 Hranjec T, Rosenberger LH, Swenson B, Metzger R, Flohr TR, Politano AD, *et al*. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. *Lancet Infect Dis* 2012;12: 774–780.
32 Karanika S, Paudel S, Zervou FN, Grigoras C, Zacharioudakis IM, Mylonakis E. Prevalence and clinical outcomes of *Clostridium difficile* infection in the intensive care unit: a systematic review and meta-analysis. *Open Forum Infect Dis* 2015;3:ofv186.
33 Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, *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;290:2588–2598.
34 Raman K, Nailor MD, Nicolau DP, Aslanzadeh J, Nadeau M, Kuti JL. Early antibiotic discontinuation in patients with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoscopy cultures. *Crit Care Med* 2013;41: 1656–1663.
35 Baggs J, Jernigan JA, Halpin AL, Epstein L, Hatfield KM, McDonald LC. Risk of subsequent sepsis within 90 days after a hospital stay by type of antibiotic exposure. *Clin Infect Dis* 2018;66:1004–1012.
36 Luther MK, Timbrook TT, Caffrey AR, Dosa D, Lodise TP, LaPlante KL. Vancomycin plus piperacillin-tazobactam and acute kidney injury in adults: a systematic review and meta-analysis. *Crit Care Med* 2018; 46:12–20.
37 Schreier DJ, Kashani KB, Sakhuja A, Mara KC, Tootooni MS, Personett HA, *et al*. Incidence of acute kidney injury among critically ill patients with brief empiric use of antipseudomonal β-lactams with vancomycin. *Clin Infect Dis* 2019;68:1456–1462.
38 Kett DH, Cano E, Quartin AA, Mangino JE, Zervos MJ, Peyrani P, *et al*.; Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (IMPACT-HAP) Investigators. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *Lancet Infect Dis* 2011;11: 181–189.
39 Dean NC, Bateman KA, Donnelly SM, Silver MP, Snow GL, Hale D. Improved clinical outcomes with utilization of a community-acquired pneumonia guideline. *Chest* 2006;130:794–799.
40 McCabe C, Kirchner C, Zhang H, Daley J, Fisman DN. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. *Arch Intern Med* 2009;169:1525–1531.
41 Frei CR, Attridge RT, Mortensen EM, Restrepo MI, Yu Y, Oramasionwu CU, *et al*. Guideline-concordant antibiotic use and survival among patients with community-acquired pneumonia admitted to the intensive care unit. *Clin Ther* 2010;32:293–299.
42 Go ES, Urban C, Burns J, Kreiswirth B, Eisner W, Mariano N, *et al*. Clinical and molecular epidemiology of acinetobacter infections sensitive only to polymyxin B and sulbactam. *Lancet* 1994;344: 1329–1332.
43 Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. *J Antimicrob Chemother* 2011;66:1223–1230.
44 Gillespie D, Francis NA, Carrol ED, Thomas-Jones E, Butler CC, Hood K. Use of co-primary outcomes for trials of antimicrobial stewardship interventions. *Lancet Infect Dis* 2018;18:595–597.
45 Banerjee R, Teng CB, Cunningham SA, Ihde SM, Steckelberg JM, Moriarty JP, *et al*. Randomized trial of rapid multiplex polymerase chain reaction-based blood culture identification and susceptibility testing. *Clin Infect Dis* 2015;61:1071–1080.
46 Sanchez-Nieto JM, Torres A, Garcia-Cordoba F, El-Ebiary M, Carrillo A, Ruiz J, *et al*. Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study. *Am J Respir Crit Care Med* 1998;157:371–376.
47 Huang DT, Yealy DM, Filbin MR, Brown AM, Chang CH, Doi Y, *et al*.; ProACT Investigators. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. *N Engl J Med* 2018;379: 236–249.
48 Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med* 2006; 355:2619–2630.
49 Trevino SE, Pence MA, Marschall J, Kollef MH, Babcock HM, Burnham CD. Rapid MRSA PCR on respiratory specimens from ventilated patients with suspected pneumonia: a tool to facilitate antimicrobial stewardship. *Eur J Clin Microbiol Infect Dis* 2017;36: 879–885.
50 He Q, Chen W, Huang L, Lin Q, Zhang J, Liu R, *et al*. Performance evaluation of three automated identification systems in detecting carbapenem-resistant Enterobacteriaceae. *Ann Clin Microbiol Antimicrob* 2016;15:40.

51 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.

52 Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, *et al*. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006;174:84–93.

53 Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, *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: 463–474.

54 Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med* 2008;177: 498–505.

55 Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, *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.

56 Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, *et al*.; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44: S27–S72.

57 Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, *et al*. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). *Eur Respir J* 2017; 50:1700582.

58 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. *Intensive Care Med* 2017;43: 304–377.

59 Vanderkooi OG, Low DE, Green K, Powis JE, McGeer A; Toronto Invasive Bacterial Disease Network. Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin Infect Dis* 2005; 40:1288–1297.

60 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.

61 American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388–416.

62 Shindo Y, Ito R, Kobayashi D, Ando M, Ichikawa M, Shiraki A, *et al*. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2013; 188:985–995.

63 Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, *et al*.; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* 2015;373: 415–427.

64 Aliberti S, Reyes LF, Faverio P, Sotgiu G, Dore S, Rodriguez AH, *et al*.; GLIMP investigators. Global Initiative for Meticillin-resistant *Staphylococcus aureus* Pneumonia (GLIMP): an international, observational cohort study. *Lancet Infect Dis* 2016;16: 1364–1376.

65 Restrepo MI, Babu BL, Reyes LF, Chalmers JD, Soni NJ, Sibila O, *et al*.; GLIMP. Burden and risk factors for *Pseudomonas aeruginosa* community-acquired pneumonia: a multinational point prevalence study of hospitalised patients. *Eur Respir J* 2018;52: 1701190.

66 Attridge RT, Frei CR, Restrepo MI, Lawson KA, Ryan L, Pugh MJ, *et al*. Guideline-concordant therapy and outcomes in healthcare-associated pneumonia. *Eur Respir J* 2011;38: 878–887.

67 Haas MK, Dalton K, Knepper BC, Stella SA, Cervantes L, Price CS, *et al*. Effects of a syndrome-specific antibiotic stewardship intervention for inpatient community-acquired pneumonia. *Open Forum Infect Dis* 2016;3:ofw186.

68 Dean NC, Jones BE, Jones JP, Ferraro JP, Post HB, Aronsky D, *et al*. Impact of an electronic clinical decision support tool for emergency department patients with pneumonia. *Ann Emerg Med* 2015;66: 511–520.

69 Jones BE, Brown KA, Jones MM, Huttner BD, Greene T, Sauer BC, *et al*. Variation in empiric coverage versus detection of methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* in hospitalizations for community-onset pneumonia across 128 US Veterans Affairs medical centers. *Infect Control Hosp Epidemiol* 2017; 38:937–944.

70 Berger A, Edelsberg J, Oster G, Huang X, Weber DJ. Patterns of initial antibiotic therapy for community-acquired pneumonia in U.S. hospitals, 2000 to 2009. *Am J Med Sci* 2014;347:347–356.

71 Richter SS, Diekema DJ, Heilmann KP, Dohrn CL, Riahi F, Doern GV. Changes in pneumococcal serotypes and antimicrobial resistance after introduction of the 13-valent conjugate vaccine in the United States. *Antimicrob Agents Chemother* 2014;58: 6484–6489.

72 Prina E, Ranzani OT, Polverino E, Cilloniz C, Ferrer M, Fernandez L, *et al*. Risk factors associated with potentially antibiotic resistant pathogens in community-acquired pneumonia. *Ann Am Thorac Soc* 2015;12:153–160.

73 von Baum H, Welte T, Marre R, Suttorp N, Ewig S; CAPNETZ study group. Community-acquired pneumonia through Enterobacteriaceae and *Pseudomonas aeruginosa*: diagnosis, incidence and predictors. *Eur Respir J* 2010;35:598–605.

74 Gillet Y, Vanhems P, Lina G, Bes M, Vandenesch F, Floret D, *et al*. Factors predicting mortality in necrotizing community-acquired pneumonia caused by *Staphylococcus aureus* containing Panton-Valentine leukocidin. *Clin Infect Dis* 2007;45: 315–321.

75 Lobo LJ, Reed KD, Wunderink RG. Expanded clinical presentation of community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia. *Chest* 2010;138:130–136.

76 Griffin AT, Peyrani P, Wiemken TL, Ramirez JA, Arnold FW. Empiric therapy directed against MRSA in patients admitted to the intensive care unit does not improve outcomes in community-acquired pneumonia. *Infection* 2013;41:517–523.

77 van der Eerden MM, Vlaspolder F, de Graaff CS, Groot T, Bronsveld W, Jansen HM, *et al*. Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomised study. *Thorax* 2005;60:672–678.

78 Self WH, Grijalva CG, Williams DJ, Woodworth A, Balk RA, Fakhran S, *et al*. Procalcitonin as an early marker of the need for invasive respiratory or vasopressor support in adults with community-acquired pneumonia. *Chest* 2016;150:819–828.

79 Rothberg MB, Zilberberg MD, Pekow PS, Priya A, Haessler S, Belforti R, *et al*. Association of guideline-based antimicrobial therapy and outcomes in healthcare-associated pneumonia. *J Antimicrob Chemother* 2015;70:1573–1579.

80 Soo Hoo GW, Wen YE, Nguyen TV, Goetz MB. Impact of clinical guidelines in the management of severe hospital-acquired pneumonia. *Chest* 2005;128:2778–2787.

81 Ioannidis JP, Lau J. State of the evidence: current status and prospects of meta-analysis in infectious diseases. *Clin Infect Dis* 1999;29: 1178–1185.

82 Kollef MH, Kollef KE. Antibiotic utilization and outcomes for patients with clinically suspected ventilator-associated

pneumonia and negative quantitative BAL culture results. *Chest* 2005; 128:2706–2713.
83 Cowley MC, Ritchie DJ, Hampton N, Kollef MH, Micek ST. Outcomes associated with de-escalating therapy for methicillin-resistant *Staphylococcus aureus* in culture-negative nosocomial pneumonia. *Chest* 2019;155:53–59.
84 Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stéphan F, *et al*. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med* 2000;132:621–630.
85 Meduri GU, Mauldin GL, Wunderink RG, Leeper KV Jr, Jones CB, Tolley E, *et al*. Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. *Chest* 1994;106:221–235.
86 Pulido MR, Moreno-Martinez P, Gonzalez-Galan V, Fernandez Cuenca F, Pascual A, Garnacho-Montero J,*et al.*; MagicBullet Working Group. Application of BioFire FilmArray blood culture identification panel for rapid identification of the causative agents of ventilator-associated pneumonia. *Clin Microbiol Infect* 2018;24: 1213.e1–1213.e4.
87 Weiss E, Zahar JR, Garrouste-Orgeas M, Ruckly S, Essaied W, Schwebel C, *et al*.; OUTCOMEREA Study Group. De-escalation of pivotal beta-lactam in ventilator-associated pneumonia does not impact outcome and marginally affects MDR acquisition. *Intensive Care Med* 2016;42:2098–2100.
88 Kollef MH, Chastre J, Clavel M, Restrepo MI, Michiels B, Kaniga K, *et al*. A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. *Crit Care* 2012;16: R218.
89 Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. *J Allergy Clin Immunol* 2014;133:790–796.
90 Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA* 2019;321:188–199.
91 Plataki M, Kashani K, Cabello-Garza J, Maldonado F, Kashyap R, Kor DJ, *et al*. Predictors of acute kidney injury in septic shock patients: an observational cohort study. *Clin J Am Soc Nephrol* 2011;6: 1744–1751.
92 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.
93 Iscimen R, Cartin-Ceba R, Yilmaz M, Khan H, Hubmayr RD, Afessa B, *et al*. Risk factors for the development of acute lung injury in patients with septic shock: an observational cohort study. *Crit Care Med* 2008; 36:1518–1522.
94 Kojicic M, Li G, Hanson AC, Lee KM, Thakur L, Vedre J, *et al*. Risk factors for the development of acute lung injury in patients with infectious pneumonia. *Crit Care* 2012;16:R46.
95 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.
96 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.
97 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.
98 Montravers P, Tubach F, Lescot T, Veber B, Esposito-Farèse M, Seguin P, *et al*.; DURAPOP Trial Group. Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial. *Intensive Care Med* 2018;44:300–310.
99 Klein Klouwenberg PM, Cremer OL, van Vught LA, Ong DS, Frencken JF, Schultz MJ, *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.