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SUPPLEMENT ARTICLE

Antimicrobial Treatment Duration in Sepsis and Serious Infections

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Sepsis mortality has improved following advancements in early recognition and standardized management, including emphasis on early administration of appropriate antimicrobials. However, guidance regarding antimicrobial duration in sepsis is surprisingly limited. Decreased antibiotic exposure is associated with lower rates of de novo resistance development, *Clostridioides difficile*-associated disease, antibiotic-related toxicities, and health care costs. Consequently, data weighing safety versus adequacy of shorter treatment durations in sepsis would be beneficial. We provide a narrative review of evidence to guide antibiotic duration in sepsis. Evidence is significantly limited by noninferiority trial designs and exclusion of critically ill patients in many trials. Potential challenges to shorter antimicrobial duration in sepsis include inadequate source control, treatment of multidrug-resistant organisms, and pharmacokinetic alterations that predispose to inadequate antimicrobial levels. Additional studies specifically targeting patients with clinical indicators of sepsis are needed to guide measures to safely reduce antimicrobial exposure in this high-risk population while preserving clinical effectiveness.

Keywords. sepsis; infection; antibiotic; duration; length.

Sepsis mortality has declined significantly over the past 30 years, driven largely by improvements in early recognition and standardized management approaches [1, 2]. While the nuances of some management strategies in sepsis such as fluid resuscitation [3], serial laboratory monitoring [4–6], and corticosteroids [7, 8] are still being debated, the timely initiation of appropriate antibiotic therapy remains an uncontested hallmark of successful sepsis treatment. Myriad studies have highlighted the value of appropriate (in vitro-active) empiric antibiotic choices in sepsis [9–11] and their early initiation, especially in septic shock [12–15], and have even led to inclusion of early antibiotic administration in national quality metrics to compare hospital performance [16, 17]. However, guidance is surprisingly limited regarding the optimal duration of therapy for patients with sepsis. The current Surviving Sepsis Campaign (SSC) guideline makes a general recommendation that 7 to 10 days of antibiotic coverage is likely sufficient for most serious infections associated with sepsis and septic shock, although this course may be lengthened in some scenarios (eg, undrained foci of infection, *Staphylococcus aureus* bacteremia, and neutropenia) or shortened in others (eg, pyelonephritis and spontaneous bacterial peritonitis) [18]. The recommendation is graded as weak, with low-quality evidence, supported specifically by data from treatment trials (predominantly in pneumonia [19–21], and intraabdominal [22] and urinary tract infections [23]) with limited representation of patients with sepsis and septic shock.

In principle, the optimal duration of antibiotic therapy in sepsis would be one that maximizes clinical effectiveness while minimizing the antibiotic-associated risks such as toxicities, *Clostridioides difficile*-associated disease, and emergence of resistance, as well as health care costs. There are many host- and pathogen-specific determinants impacting the required duration of antibiotic therapy in sepsis, and extrapolation from healthier populations may be overly simplistic. Conspicuously few studies have investigated the optimal duration of antibiotic therapy in critically ill populations. Indeed, even the landmark sepsis trials which have shaped sepsis management over the last 2 decades [4–6, 24–26] did not report any specific antibiotic regimens, durations, or evidence of microbiologic cure in populations with culture-positive sepsis. As such, it is not surprising that usual care durations of antibiotic therapy for sepsis and serious infections remain highly variable [27]. A survey of health care professional users of a sepsis crowdsourcing application recently revealed an average reported duration of intravenous antibiotic therapy for sepsis of more than 10 days for 17%, 7–10 days for 40%, 5–7 days for 27%, and 3–5 days for 13% of respondents [28].

The mortality risk in sepsis is substantial and the margin for error small. Bedside providers have until recently been relatively complacent with longer courses of therapy, potentially due to the false sense of security it may offer for sicker patients. However, a paradigm change has occurred in recent years [29] and the importance and need for antibiotic stewardship is well

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recognized across the spectrum of providers and disciplines. In a retrospective cohort study of 7118 patients with severe sepsis or septic shock, Teshome et al [30] reported a 4% increased risk of de novo antibiotic resistance for each additional day of antipseudomonal β-lactam exposure, highlighting the importance of striving to determine and implement the minimum necessary duration of therapy, even in sepsis. Furthermore, recent data from Rhee et al demonstrated that among patients with culture-proven sepsis treated with adequate empiric antibiotics, treatment with overly broad-spectrum antibiotics was associated with a 20% increase in the odds of death, with a median (interquartile range [IQR]) duration of treatment of 4 (2–6) days for both antipseudomonal β-lactams and carbapenems [31]. Given that the evidence base is currently insufficient to perform a systematic review in search of the optimal duration of antibiotic treatment in sepsis, we instead provide a narrative review of the existing literature, which can be leveraged to inform the current practice of antibiotic therapy in sepsis, focusing specifically on the optimal duration rather than choice of antimicrobial therapy.

IS SHORTER ALWAYS BETTER?

The first step to determining the optimal duration of therapy in sepsis and serious infections is to understand the origins of our usual care standard. Much of our modern antibiotic prescribing practice has been based largely on expert opinion and influenced to an extent by historical lessons learned from the treatment of tuberculosis. For the latter, success was directly linked to duration and resistance could occur in setting of inappropriate dosing or monotherapy [32]. Early studies in patients with cystitis noted that single-dose therapy was suboptimal compared to multiday therapy [33], establishing that most serious infection would presumably at least require multiple days of antibiotics. Regimens for acute bacterial infections evolved to prolonged courses with the rationale of reducing relapses and emergence of resistance from undertreated infections [34]. However, this evolution was based on a weak evidence base (small studies, heterogenous populations, and subjective metrics for clinical response) and was often arbitrary with a peculiar penchant for 7-day increments [35]. This led to many previous iterations of practice guidelines recommending iterative courses such as 1–2 weeks for community-acquired pneumonia [36], 2 weeks for pyelonephritis [33], and 3–4 weeks for bacteremia [34].

Recent years have seen a consistent trend toward shorter antibiotic treatment durations for many infectious syndromes including pneumonia (community-acquired and nosocomial), cystitis, complicated urinary tract infections, intraabdominal infection, acute bacterial sinusitis, cellulitis and soft tissue infection, septic arthritis, and chronic osteomyelitis [29, 35]. Some examples of these studies are listed in Table 1. In fact, there are now several examples in the "shorter is better" literature of reduced treatment durations for each of these conditions, which have significantly changed practice in the last decade. These data present consistent themes of preserved treatment efficacy with fewer antibiotic days and reduced adverse events. Below are a few studies that have significantly contributed to the paradigm change toward shorter durations of antibiotic therapy. We have limited the focus of this review predominantly to clinical trials rather than observational studies given that observational studies are biased towards better outcome in those with early discontinuation (see Table 1 for additional details on relevant studies).

- Ventilator-associated pneumonia (VAP): In 2003, Chastre et al [19] published a landmark trial demonstrating that 8 days of antibiotic treatment for VAP was noninferior to 15 days for 28-day mortality and infection recurrence for all organisms except for nonfermenting gram-negative bacilli including *Pseudomonas aeruginosa*.
- Community-acquired pneumonia (CAP): Dunbar et al [37] demonstrated noninferior clinical response of short-course, higher-dose levofloxacin (750 mg for 5 days) compared with a longer course at a lower dose (500 mg for 10 days) as well as improved symptoms and defervescence in the intervention arm. This study was followed by several others investigating other regimens. In a 2016 study of adults hospitalized for CAP, Uranga et al [38] found that a short course of 5 days of physician-determined antibiotics was noninferior to a physician-determined longer course with regard to clinical cure at 10 and 30 days, CAP symptoms, and 30-day mortality, and also found that the shorter-course patients had fewer readmissions within 30 days. The current guidelines on diagnosis and treatment of CAP have incorporated these data into their recommendation of 5 days of antibiotic duration for all patients provided that they have demonstrated clinical improvement and were not diagnosed with either *P. aeruginosa* or methicillin-resistant *Staphylococcus aureus*, for which they recommend 7 days [48].
- Complicated urinary tract infection (cUTI): In a 2008 study of patients with acute pyelonephritis or cUTI, 5 days of high-dose levofloxacin was noninferior to 10 days of ciprofloxacin for microbiologic eradication and clinical success [40]. Subsequently, in a study of women with community-acquired pyelonephritis, 7 days of ciprofloxacin was noninferior to 14 days in clinical and microbiologic efficacy measures and longer-course therapy was associated with more oral candidiasis [41].
- Neutropenic fever: In a 2017 study of high-risk neutropenic fever patients without a microbiologically diagnosed infection, empiric antimicrobial therapy was safely discontinued after 72 hours of apyrexia in the intervention group compared to the control group in which empiric antimicrobial

Table 1. Trials of Reduced Antimicrobial Durations in Multiple Infectious Syndromes

Infectious Syndrome	Author	Study Design	Primary Outcome	No. of Patients	Inclusion Criteria	Exclusion Criteria	Patient Location	Severity of Illness	Short Course Antibiotic: Duration, d	Long Course Antibiotic: Duration, d	Outcomes	Comments
VAP	Chastre et al 2003 [19]	Multicenter, noninferiority RCT	28-d mortality; microbiologically documented PNA recurrence; abx-free days	197	MV > 48 h; clinical suspicion of VAP; positive distal airway culture; appropriate abx within 24 h of culture	SAPSII > 65; immunosuppression or long-term corticosteroid therapy; concomitant extrapulmonary infection requiring >8 d abx	ICU	Short course: SAPSII 45 (SD, 15), SOFA 7.3 (4); vasopressors 33% long course: SAPSII 45 (15), SOFA 7.4 (4); vasopressors 35%; mechanical ventilation 100%	Adequate abx per physician discretion: 8	Adequate abx per physician discretion: 15	Primary ARRs: all-cause mortality 1.6 (90% CI, −3.7 to 6.9); pulmonary infection recurrence 2.9 (− 3.2 to 9.1); abx-free days 4.4 (3.1–5.6)	Noninferiority met
CAP	Dunbar et al 2003 [37]	Multicenter, double-blind, noninferiority RCT	Clinical response at follow-up; 7–14 d post medication completion	530	Mild-to-severe CAP	Levofloxacin-resistant organism; previous quinolone treatment failure; life expectancy < 72 h; neutropenia or HIV; empyema or effusion requiring chest tube	Inpatient or outpatient	PSI class I/II 58%; class III/IV 42%	Levofloxacin 750 mg: 5	Levofloxacin 500 mg: 10	Clinical success rate 92.4% vs 91.1%	Noninferiority met; short course (higher dose) group defervescence earlier than that longer course
CAP	Uranga et al 2016 [38]	Multicenter, noninferiority RCT	Clinical cure at 10 d; clinical cure at 30 d; CAP symptoms at 5 d and 10 d	312	Hospitalization for CAP	ICU admission before randomization; immunosuppression; HCAP; specific indication for longer duration; required chest tube	Ward	PSI short 81.8 (SD, 33.8); PSI long 83.7 (33.7); vasopressors 1.6%; mechanical ventilation 1%	Adequate abx per physician discretion: 5	Adequate abx and duration per physician discretion	Clinical cure 10 d: 53.6% vs 48.6%; clinical cure 30 d: 91.9% vs 88.6%; CAP symptoms 5 d: 27.2 vs 24.7; CAP symptoms 10 d: 17.9 vs 18.6	No difference in any primary outcomes; significant reduction in duration of antibiotics and hospital readmissions by 30 d
CAP; HCAP	Vaughn et al 2019 [39]	Multicenter, retrospective cohort	Rate of excess antibiotic treatment	6481	Adult medical patients with community-onset pneumonia (CAP or HCAP)	ICU admission; MV; severe immunocompromise; *Legionella* or fungal pathogen; bacteremia or empyema	Ward	qSOFA short >2 9.8% qSOFA long >2 8.8%	Adequate abx per physician discretion: 5–7	Adequate abx per physician discretion: > 5–7	Median excess duration: CAP 2 d (IQR, 0–4), HCAP 1 d (0–3)	Excess duration was only associated with patient-reported events (diarrhea, GI distress, thrush most common)
cUTI	Peterson et al 2008 [40]	Multicenter, double-blind, noninferiority RCT	Microbiologic eradication post therapy	1093	Acute pyelonephritis or cUTI	Complete obstruction; surgery or lithotripsy within 7 d; abx therapy for concurrent infection; quinolone-resistant pathogen; abscess, prostatitis, epidymitis	Inpatient or outpatient	NR	Levofloxacin 750 mg: 5	Ciprofloxacin 400/500 mg: 10	Microbiologic eradication: 79.8% vs 77.5%	Noninferiority met; clinical success comparable between groups

Table 1. Continued

Infectious Syndrome	Author	Study Design	Primary Outcome	No. of Patients	Inclusion Criteria	Exclusion Criteria	Patient Location	Severity of Illness	Short Course Antibiotic: Duration, d	Long Course Antibiotic: Duration, d	Outcomes	Comments
cUTI	Sandberg et al 2012 [41]	Multicenter, double-blind, noninferiority RCT	Clinical and bacteriologic efficacy 10–14 d after treatment	156	Women with diagnosis of community-acquired pyelonephritis	Systemic abx within 72 h; indwelling or intermittent bladder catheterization; CrCl < 0.5 mL/s	Inpatient or outpatient	NR	Ciprofloxacin 500 mg: 7	Ciprofloxacin 500 mg: 14	Clinical cure: 97% vs 96%	Noninferiority met; long course significantly higher rate of oral candidiasis
NF	Aguilar-Guisado et al 2017 [42]	Multicenter, open, superiority RCT	Number of EAT-free days	157	Hematologic malignancies or HSCT with febrile neutropenia without microbiologic diagnosis	Microbiologic diagnosis of infection or noninfectious etiology for fever; CrCl < 30 mL/min; receiving antibiotics for any reason prior to NF onset	Ward	NR	72 h apyrexia, symptom resolution and normal vital signs	Apyrexia, symptom resolution, normal vital signs AND neutropenia resolved	Mean EAT-free days: 16.1 (SD, 6.3) vs 13.6 (7.2)	Mean fever days and all-cause mortality was not different; control group had more grade 3–4 adverse events than the short course
BSI	Daneman et al 2018 [43]	Multicenter, open pilot RCT	Feasibility (recruitment, adherence)	115	Positive blood culture result with pathogenic bacteria while in ICU	Immunocompromise; prosthetic heart valve or endovascular grafts; established requirement for extended treatment; *Staphylococcus aureus* or fungal BSI	ICU	APACHEII 22 (IQR, 18–26); vasopressors 52%	Adequate abx per physician discretion: 7	Adequate abx per physician discretion: 14	Median recruitment rate 0.7 patients/mo (IQR, 0.3– 1.5); median adherence 71% (50%–85%)	90-d mortality 15%, ICU mortality 7%, hospital mortality 13%; duration MV 8 d (3–21); relapse BSI 4%; CDI 4%; secondary AMR infection 9%
BSI	Yahav et al 2019 [44]	Mulicenter, open, noninferiority RCT	Composite: 90-d mortality, clinical failure, readmission, or LOS >14 d	604	Hospitalized adults with gram-negative bacteremia surviving to day 7 of treatment and clinically stable	Uncontrolled source; polymicrobial infection; immunosuppression	Ward; ICU	Presentation SOFA: short course 2 (IQR, 1–3), long 2 (1–3) Randomization SOFA: short 1 (0–2), long 2 (0–2)	Adequate abx per physician discretion: 7	Adequate abx per physician discretion: 14	Primary composite: risk difference −2.6 (CI, −10.5 to 5.3)	Noninferiority met; secondary endpoints not different except time to return to baseline activity, duration of antibiotic therapy, and total antibiotic days (P < .001)
IAI	Sawyer et al 2015 [22]	Multicenter, open, superiority RCT	Composite: surgical site infection, recurrent IAI, 30-d mortality	518	Complicated IAI having undergone an intervention for source control	Inadequate source control; high likelihood of death within 72 h; SBP	NR	APACHE II: 10.1 ± 0.3 (range 0–29)	Adequate abx per physician discretion: 4 after source control	Adequate abx per physician discretion: 2 after resolution of SIRS	Primary composite: ARR −0.5% (CI, −7.0% to 8.0%; P = .92)	Secondary: no difference except for duration of therapy and abx-free days
ABSSTI	Prokocimer et al 2013 [45]	Multinational, double-blind, noninferiority RCT	Early clinical response at 48–72 h assessment	667	Skin or soft tissue infection accompanied by regional or systemic signs of infection; gram-positive organism suspected/documented	Uncomplicated ABSSTI or association with prosthetic device or vascular catheter site, gram-negative pathogen suspected or documented (unless wound infection); any necrotizing process; septic shock or severe sepsis; immunosuppression	NR	NR	Tedizolid PO: 6	Linezolid: 10	Early clinical response: 79.5% vs 79.4%	Noninferiority was met for primary and secondary endpoints

Table 1. Continued

Infectious Syndrome	Author	Study Design	Primary Outcome	No. of Patients	Inclusion Criteria	Exclusion Criteria	Patient Location	Severity of Illness	Short Course Antibiotic: Duration, d	Long Course Antibiotic: Duration, d	Outcomes	Comments
ABSSTI	Moran et al 2014 [46]	Multinational, double-blind, noninferiority RCT	Early clinical response at 48–72 h assessment	666	Skin or soft tissue infection accompanied by regional or systemic signs of infection; gram-positive organism suspected/ documented	Uncomplicated ABSSTI or associated with prosthetic device or vascular catheter site; gram-negative pathogen suspected or documented (unless wound infection); any necrotizing process; septic shock or severe sepsis; immunosuppression	NR	NR	Tedizolid IV to PO: 6	Linezolid: 10	Early clinical response: 85% vs 83%	Noninferiority was met for primary and secondary endpoints
Acute pyogenic osteomyelitis	Bernard et al 2015 [47]	Multicenter, open, noninferiority RCT	Clinical cure 1 y posttreatment	359	Microbiologically confirmed pyogenic vertebral osteomyelitis	Life expectancy < 1 y; fungal, brucellar, mycobacterial infection; death within 1 wk of treatment	NR	NR	Adequate abx per physician discretion: 42	Adequate abx per physician discretion: 84	Clinical cure: 90.9% vs 90.9%	Noninferiority met

Abbreviations: ABSSTI, acute bacterial skin and soft tissue infection; abx, antibiotics; AMA, against medical advice; AMR, antimicrobial resistance; APACHE II, acute physiology + age points + chronic health points score; ARR, absolute risk reduction; BSI, bloodstream infection; CAP, community-acquired pneumonia; CI, confidence interval; CrCl, creatinine clearance; cUTI, complicated urinary tract infection; CVC, central venous catheter; DFI, diabetic foot infection; EAT, empiric antibiotic therapy (consisted of antipseudomonal β-lactam monotherapy or in combination with other agents per institutional protocol); EOT, end of therapy; HCAP, health care-associated pneumonia; HIV, human immunodeficiency virus; HSCT, hematopoetic stem cell transplantation; IAI, intraabdominal infection; ICU, intensive care unit; IQR, interquartile range; ITT, intention to treat; LOS, length of stay; MV, mechanical ventilation; NF, neutropenic fever; NR, not reported; PD, peritoneal dialysis; PNA, pneumonia; PSI, pneumonia severity index; qSOFA, quick sequential organ failure assessment score; RCT, randomized controlled trial; SAPS II, simplified acute physiology score; SBP, spontaneous bacterial peritonitis; SOFA, sequential organ failure assessment score.
Number of patients diagnosed with sepsis not reported but number of patients for whom sepsis was the reason for MV was reported.

therapy was continued until 72 hours of apyrexia and resolution of neutropenia. The intervention group had significantly greater antibiotic-free days while mean fever days and all-cause mortality was not different between the groups [42].

- Bloodstream infection (BSI): In a recent study of hospitalized patients with gram-negative bacteremia surviving and clinically stable at day 7, 7 days of antibiotic therapy was noninferior to 14 days for the composite endpoint of 90-day mortality, clinical failure, or hospital length of stay [44]. Even in such highly morbid infections as *S. aureus* bacteremia there has been a sequential reduction in the number of weeks recommended for therapy. *S. aureus* bacteremia was historically treated for a standard 4–6 weeks of intravenous therapy [49], until a subgroup of "uncomplicated" *S. aureus* bacteremia was identified for whom 2–4 weeks became accepted [50]. Now, a trial is underway to evaluate just 7 days of therapy in uncomplicated *S. aureus* bacteremia [51]. In another approach, Holland et al recently published a successful approach to protocolizing the treatment durations of multiple clinically diverse staphylococci BSIs. This approach resulted in a noninferior rate of clinical success paired with 29% reduction in median antibiotic duration without any increase in infection-related adverse events [52]. Although it should be noted that this trial enrolled both *S. aureus* and coagulase-negative staphylococci infections, which have very different clinical outcomes, and the study was not powered to adequately study individual subgroups. Additionally, the data on which the protocol methodology were based were often low-quality evidence due to the limited availability of randomized trials testing antibiotic treatment durations in BSI [53]. Despite these limitations, this approach provides another potential tool in the stewardship toolkit.
- Intraabdominal infections (IAIs): The 2015 STOP-IT trial [22] significantly impacted the practice for managing IAIs. Patients with IAI undergoing source control intervention were randomized to receive antibiotics for either 4 days after source control (intervention arm) or 2 days after resolution of systemic inflammatory response symptoms, which ended up being a median of 8 (IQR, 5–10) days. There was no difference in the primary composite endpoint of mortality, surgical site infection, or recurrent IAI, but the intervention arm received significantly shorter duration of therapy with greater antibiotic-free days. Of note, the mean age in this population was 52 years, and the mean APACHE II score (acute physiology + age points + chronic health points) was relatively low at 10.1 (predicted mortality approximately 10%) compared to the average hospitalized patients with abdominal sepsis.
- Acute bacterial skin and soft tissue infections (ABSSTIs): The ESTABLISH studies investigated the use of tedizolid for ABSSTIs. In both studies, 6 days of tedizolid (either oral or

intravenous to oral) was noninferior to 10 days of linezolid for clinical response [45, 46].

- Acute bacterial osteomyelitis: Bernard et al [47] demonstrated noninferiority of 6 vs 12 weeks of antibiotics in the primary analysis of 1-year clinical cure. However, the noninferiority margin was not met for the subgroup analyses of age over 75, non-*S. aureus* infection, immunosuppression, diabetes, and presence of neurologic signs, abscess, or endocarditis.

Despite these exciting results, it must be noted that many of these data are derived from noninferiority studies and with broad exclusion criteria that tended to restrict the final study population to those with milder acute illness and fewer underlying high-risk illnesses (Table 1). While a noninferiority trial design may be a reasonable means for investigating new antibiotic durations in select circumstances, it has important limitations [54, 55]. Historical trial data used to establish the magnitude of the effect of standard therapy or active control (vs placebo) relies on the "constancy" assumption. However, historical data may not reflect the current landscape of patient complexity and patient care practices [56]. Furthermore, noninferiority of a new therapy to an active control does not necessarily confirm superiority of the new therapy over placebo, and the sample size for noninferiority trials is unfortunately often influenced by arbitrary thresholds of clinical importance and trial sponsor budget.

Importantly, the majority of the antibiotic treatment duration studies either specifically excluded patients with sepsis or intensive care unit (ICU) admission or did not provide demographic information such as the frequency of sepsis diagnosis, vasopressor or ventilatory support, or severity of illness scores. Therefore, by limiting the inclusion criteria to a patient population with a lower severity of illness, the event rates for mortality or serious complications are decreased, and the trial may be biased toward noninferiority, particularly if the prespecified margin is large. Additional common exclusion criteria limiting applicability of these data include renal dysfunction, immunocompromising conditions, and recent antibiotic use, which are all relatively common in real-world critically ill populations.

CAN ORGAN-SPECIFIC INFECTION TREATMENT DURATIONS BE EXTRAPOLATED TO SEPSIS?

There is a notable lack of trials on the duration of antibiotic therapy in sepsis. As previously mentioned, none of the landmark sepsis trials which have shaped current sepsis management [4–6, 24–26] reported any specific antibiotic regimens, durations, or microbiologic data. The PROWESS [24] and PROWESS-SHOCK [25] protocol did not call for any standardized approach to critical care management, including antibiotics, and no data were provided on the frequency, classes, or duration of prescribed antibiotics. Later, the ACCESS [26] and ProCESS [4] trials only reported high rates of "appropriate antibiotic administration," and ARISE [6] reported a median time to antibiotic administration of 70 and 67 minutes in their experimental and control groups, respectively. Furthermore, critically ill patients are underrepresented in trials evaluating the optimal duration of antibiotic treatment in organ-specific infections such as pneumonia and urinary tract infections. In the absence of truly representative data, we must ask ourselves 2 questions: Do sicker patients in fact warrant longer courses of antibiotics? And is it reasonable to extend the findings of studies in patients with infection to those with sepsis? Infection is necessary but not sufficient for the definition of sepsis. Due to the complexity of organ dysfunction in sepsis, observed morbidity does not bear a linear relationship with microbial burden, and the risk of mortality is not entirely mitigated by optimal antimicrobial management. Unfortunately, relatively few trials have been conducted specifically in the critically ill or in serious infections with a high likelihood of systemic manifestations. One example is the aforementioned Chastre et al study of antibiotic duration in VAP [19]. Inclusion criteria required ICU admission and mechanical ventilation for at least 48 hours, and approximately one-third of the patients received vasopressor support. The authors found 8 days of antibiotics to be noninferior to 15 days with regard to all-cause mortality and infection recurrence, which greatly changed treatment guidelines [21, 57, 58]. Although it should be noted that here, too, exclusion criteria included a simplified acute physiology score (SAPS II) greater than 65 (which correlates to approximately 75% mortality), and immunocompromising conditions such as neutropenia, AIDS, and immunosuppressant or long-term corticosteroid therapy. Yahav et al [44] conducted an open-label noninferiority study of hospitalized patients with uncomplicated gram-negative bacteremia receiving 7 vs 14 days of antibiotic therapy. The noninferiority margin was met; however, the mean baseline sequential organ failure assessment (SOFA) score was lower than would be expected in gram-negative BSI in both groups. Additionally, in order to be randomized at day 7, the patients in this study had to be clinically stable, thus there were no patients in shock or mechanical ventilation at that time, and these frequencies were not reported at presentation. More specific to the critically ill population, Daneman et al [43] have published a pilot study of bacteremic ICU patients with high median APACHE II scores (22; IQR, 18–26) and vasopressor support (52%), in which they demonstrated feasibility and good adherence to the study protocol. We anxiously await the results of their complete randomized controlled trial appropriately powered to examine the 7 vs 14 day treatment duration in bacteremic shock for noninferiority in the primary outcome of 90-day mortality and several relevant secondary outcomes.

Logically, it seems safer to discontinue antibiotics earlier in septic patients who demonstrate clinical stability by the time culture results are available compared to those who remain unstable. However, given the limited data in critically ill patients

on this topic to date, there are several important factors to be considered before routinely accepting shorter antibiotic courses, even for clinically stable septic patients. Some of these will be examined below.

Severity of Illness

In multiple treatment guidelines, severity of illness is used as a tool to guide the choice and timing of the initial empiric antibiotic regimen whereas recommendations on ultimate duration are based on the organism cultured and the primary organ-system involved [21, 48, 59]. However, in clinical practice, allowance is often given for the patient to demonstrate signs of clinical improvement before an ultimate duration is chosen, which itself predisposes to longer treatment durations associated with greater severity of illness [60]. The 2019 CAP guidelines' recommendation on duration states that most patients should be treated for a *minimum* of 5 days, with discontinuation at that point considered only if the patient has been achieved clinical stability [48]. However, the authors endorse longer courses for pneumonia complicated by deep-seated infections as well as less common organisms not covered by the guideline (eg, *Burkholderia pseudomallei*, *Mycobacterium tuberculosis*, and endemic fungi). Interestingly, Aliberti et al [61] evaluated whether the 2005 recommendations (similar to those above) were utilized by treating physicians to tailor duration of therapy based upon disease severity or clinical response. The mean ± standard deviation treatment duration was 11 ± 4.7 days, with 42% of patients receiving a course of 10–14 days. Significantly, time to clinical stability was not associated with *total* length of therapy, but it was associated with the duration of intravenous therapy. This is likely related to sicker patients spending longer in the hospital, during which time the default route of administration is generally intravenous. Interestingly, while severity of illness scores were not associated with length of therapy, surrogate markers including admission to the ICU, hypotension, and acidemia were associated with significantly longer durations. Earlier transition to oral step-down therapy was also found to be safe in a recent observational study of patients with Enterobacteriaceae bacteremia who attained clinical stability by day 5 [62]. As such, there is not a clear-cut association between severity of illness and required length of therapy, but providers appear to have more confidence in transitioning to oral therapy earlier in less severely ill patients.

Source Control—Overt and Occult

Source control of septic foci has long been recognized as a key intervention in the nonantimicrobial management of sepsis [63–65], and typically refers to procedures such as draining infected fluid collections, debriding infected tissues, removing infected devices or foreign materials, and correction of anatomic abnormalities which either predispose to microbial contamination or reduce antimicrobial exposure. On a macroscopic level, these procedures reduce microbial burden and facilitate antibiotic penetration into sequestered sites, which could otherwise serve as reservoirs of persistent infection and acquisition of drug resistance. The importance of source control is weighted in the SSC guidelines as a best practice statement, with emphasis on early implementation as soon as medically and logistically feasible [18]. Inability to achieve control of a known source is an accepted indication for extending duration of therapy, and indeed nearly all trials of shortened treatment durations have explicitly excluded patients with an uncontrolled source or those requiring active drainage.

Expanding on the traditional concept of source control, there is now evidence that the immunologic milieu of sepsis results in an immune dysregulated state characterized by an inability to clear septic foci, as well as widespread lymphocyte apoptosis, reduced inflammatory cytokine production, and increased susceptibility to secondary infections [66, 67]. An autopsy study of 235 ICU patients with sepsis or septic shock demonstrated an unresolved septic focus in nearly 80% of subjects [68]. This suggests that even in patients lacking an overt uncontrolled source of infection, there may yet be occult foci. The precise clinical impact of this finding is not known, but may be most significant in patients with prolonged critical illness, increased age, and comorbidities associated with increased infection risk such as diabetes mellitus, and further question our ability to extrapolate what is optimal antibiotic duration from studies on healthier patients [69, 70]. Additional evidence of this sepsis-induced immunosuppression includes the high rate of reactivation of cytomegalovirus in otherwise immune competent patients [71] as well as documented secondary infections with relatively lower-virulence organisms [72, 73]. Numerous observational studies of detailed immunophenotyping in septic patients have been published in the last decade [74–77], but these have not yet been correlated to treatment outcomes. Due to the paucity of clinical data in this arena, it is not clear whether the relative immunosuppression of sepsis could limit the efficacy of shortened antibiotic treatment durations, but it is a host factor worth considering while deciding when to discontinue antibiotics until additional evidence is available.

Microbial Characteristics

Pseudomonas spp., notably *P. aeruginosa*, have been long recognized as a difficult-to-treat pathogen. This is largely due to many intrinsic and acquired resistance mechanisms as well as a predilection for high-risk hosts, which can make eradication very difficult. Indeed, *P. aeruginosa* infections are associated with substantial mortality risk [78], and clinical decision making often changes when faced with these infections compared with other organisms. For example, following the landmark trial by Chastre et al, which has been previously discussed, standard treatment duration for VAP was reduced from 2 weeks to just 8 days for most patients [19]. However, due to a high rate

of relapse from nonfermenting gram-negative bacilli (predominantly *P. aeruginosa*), some clinicians did not reduce treatment duration for *P. aeruginosa* infections for many years. It should be noted, though, that mortality was not different between the groups and several subsequent studies did not reproduce this finding, leading to the 2016 Infectious Disease Society of America and American Thoracic Society guidelines on management of hospital-acquired and VAP to recommend a 7-day treatment course for all patients, regardless of organism [21]. Indeed the potential recurrence of infection must be weighed against the probable development of resistance with additional antibiotic exposure, leading some providers to adhere to the short course recommendation for sensitive organisms and lean toward longer courses when multidrug resistance is present [79].

S. aureus infections are complex owing to both potential drug resistance and the invasive nature of the bacterium, with significant rates of endovascular and distant site complications such as endocarditis, abscess, and vertebral osteomyelitis [80]. While a subset of "uncomplicated" *S. aureus* bacteremia patients (no evidence of endocarditis or metastases, no prostheses, rapid clearance of cultures, and defervescence) has now been identified that can be treated with shorter courses of therapy [50], complication rates remain high for this infection and diligence is needed to prevent undertreatment, relapse, and morbidity [81].

Like *P. aeruginosa* and *S. aureus*, many pathogens such as *Acinetobacter* spp., *Stenotrophomonas* spp., *Enterobacteriaceae*, and even the yeast *Candida* present a clinical challenge due to their propensity to form biofilm and seeding of secondary infection sites, which can induce antimicrobial tolerance and impair eradication. Treatment of sepsis due to gram-negative pathogens harboring difficult-to-treat resistance (ie, resistance to all first-line high-efficacy, low-toxicity antibiotics, namely β-lactams [including carbapenems] and fluoroquinolones) [82], necessitates use of second- and third-line agents such as polymyxins, aminoglycosides, and tigecycline or newer agents yet to be studied specifically in sepsis such as ceftazidime/avibactam. Guidance is limited for optimal duration of therapy for such infections and difficult-to-treat resistance is a poor prognostic marker. Consequently, most providers currently err on the side of longer courses for these infections. Furthermore, given the complexity of the patients who contract highly resistant pathogens, a detailed consideration of all host, pathogen, source, clinical response trajectories, and treatment-related factors are needed to define an adequate course for these complicated infections.

Pharmacokinetic/Pharmacodynamic Issues

The success of a defined antimicrobial course in sepsis is contingent not only on the in vitro activity of the designated agent against the pathogen and the adequacy of source control, but also on pharmacokinetic/pharmacodynamic properties such as the ability to provide an appropriate and reliable dose of the antibiotic that yields therapeutic drug levels in the blood and other affected infection sites. Unfortunately, in the critically ill population, there are numerous competing factors that may impact effective dosing, including increased or decreased renal blood flow, organ dysfunction (particularly renal and hepatic), changing volume of distribution, and initiation of mechanical support devices such as continuous renal replacement therapy or extracorporeal membrane oxygenation. Although the bactericidal property of the antibiotic has been traditionally considered an important factor in treatment success against serious infections, a recent meta-analysis of 56 trials suggest there may be no intrinsic advantage of bactericidal over bacteriostatic agents and that drug dosing and other pharmacokinetic/pharmacodynamic properties may be more important drivers of efficacy [83]. For these reasons and many others, critical care pharmacists are a crucial resource when designing an effective antimicrobial regimen for septic patients [84, 85].

Please refer to the article by Tam et al in this Supplement for additional information on the topic [86].

NOT ALL SEPSIS IS CREATED EQUAL—SPECIAL CONSIDERATIONS FOR SPECIFIC POPULATIONS

Neutropenic Sepsis

The prevalence and phenotypes of immunocompromising conditions have increased over the last several decades and may increase susceptibility to sepsis from a variety of typical or opportunistic infections, which may warrant specific management strategies. However, neutropenia particularly increases vulnerability to serious acute infections and sepsis, and notably increases morbidity and mortality risk. Roughly half of neutropenic fever episodes may be complicated by sepsis or septic shock, with an attendant mortality of 35% to 50% [87]. According to the Infectious Diseases Society of America neutropenic fever guidelines, for patients with a clinically or microbiologically documented infection, appropriate antibiotic therapy should be given at least until resolution of neutropenia (absolute neutrophil count > 500 cells/mm^3) or longer if clinically necessary. In some instances, if an appropriate treatment course has been completed prior to resolution of neutropenia, patients may resume oral prophylaxis until marrow recovery [88]. They make no specific recommendations for duration of antimicrobial regimens based upon disease severity. Interestingly, the 2017 study by Aguilar-Guisado et al [42] challenged the dogma of continuing antimicrobials in neutropenic fever until neutrophil recovery. In patients with neutropenic fever without a microbiologic diagnosis of infection, discontinuation of empiric antibiotics after 72 hours without fever resulted in no difference in mean fever days or all-cause mortality. However, it should be noted that the included population was hospital ward patients; they did not include patients with septic shock and did not report how many patients met criteria for sepsis. Extended

duration of therapy is most likely to be recommended in the setting of neutropenic sepsis due to highly resistant gram-negative organisms, mold infections, or endovascular seeding.

Culture-Negative Sepsis

Culture-negative sepsis poses a number of its own unique issues with regard to antimicrobial management. First, we emphasize that a large proportion of patients (17% in 1 study) admitted with an initial clinical diagnosis of sepsis in whom a pathogen is not ultimately identified are subsequently found to have a sepsis "mimic" (another noninfectious etiology for their illness) and do not require antibiotic therapy [89]. Restricting our discussion to those patients with true culture-negative sepsis (due to antecedent antibiotics, low culture sensitivity, fastidious organisms, lack of molecular diagnostic testing available, etc.), multiple studies have documented approximately a third of sepsis cases as culture negative [24, 90, 91]. Based on recent estimates of national sepsis incidence [2], this could account for over 500 000 cases annually, meaning that earlier discontinuation of antibiotics in culture-negative sepsis is likely to have a tremendous reduction in patient and population-level antibiotic pressure. However, determining appropriate antimicrobial management in these patients is a challenge. Without an organism against which to direct therapy, treatment courses tend to remain broad and there is no clear guidance for discontinuation. A large multicenter retrospective cohort study by Kethireddy et al [91] recently reported that culture-positive vs negative sepsis have similar survival, which is contingent on timely administration of appropriate antibiotics. However, the authors did not report on mean duration of antibiotic therapy prescribed or frequency of de-escalation from empiric regimen. In a separate single-center retrospective study, Lockhart et al investigated the duration of antibiotic treatment received by culture-negative sepsis survivors [60]. Groups were stratified into less than or equal to 3 days, 4 to 7 days, and greater than 7 days. Greater severity of illness (as measured by APACHE II scores, Charlson comorbidity index, and mechanical ventilatory support) was associated with increasing duration of treatment. Specific sites of infection (pneumonia, urinary tract, joint space, and central nervous system) were associated with longer duration, while unknown or undocumented sites of infection correlated with shorter duration. These data support an organ systems-based approach to antibiotic duration in culture-negative sepsis. The SSC guidelines do not provide a specific recommendation of a defined duration for treatment of culture-negative sepsis. However, close scrutiny of host and disease characteristics and trajectories of fever, vasopressor dependence, biomarkers, etc. may guide whether a patient may be a reasonable candidate for a duration of therapy shorter than the standard, albeit not evidence-based, 7- to 10-day recommendation for all patients with sepsis [18].

NARROWER VERSUS SHORTER—LESSONS FROM DE-ESCALATION TRIALS

If the data regarding shortened duration of therapy inadequately address critically ill populations, antimicrobial de-escalation may be another tactic to reduce the adverse effects associated with prolonged broad-spectrum antibiotic use. The SSC guidelines endorse de-escalation for patients initially prescribed multiple agents (ie, combination therapy) once the patient's condition has improved and/or cultures become available, and recommend for all septic patients that potential for de-escalation be assessed daily [18]. In order to evaluate the evidence behind this practice, Tabah et al published a systematic review and meta-analysis of antimicrobial de-escalation specifically in septic ICU patients [92]. While the definition of de-escalation varied over the 14 included studies, all studies described a narrowing of the spectrum of coverage. Thirteen studies de-escalated by decreasing the number of prescribed antimicrobials and 4 included a shortening of the duration of therapy. Documentation of culture data, a lower baseline severity of illness, and clinical improvement increased the rate of de-escalation. Pertinently, infection with a multidrug-resistant organism significantly reduced the likelihood of de-escalation in several studies, as did polymicrobial infection and infections with a risk of undiagnosed pathogens (eg, IAI). Similarly, a prospective cohort study by Salahuddin and colleagues [93] found that failure to de-escalate was predicted by SAPS II score, hematologic malignancy, and isolation of multidrug-resistant organisms. None of the 14 studies reported worsened survival with de-escalation, and in the pooled mortality analysis provided there was a protective effect of de-escalation (relative risk, 0.68; 95% confidence interval, .52–.88), with moderate heterogeneity ($I^2 = 44\%$) [92]. Interestingly, de-escalation was not associated with decreased duration of therapy, although 1 study did report fewer days of antipseudomonal β-lactam and broad-spectrum gram-positive antibiotics associated with de-escalation [94]. Indeed, a recently published European position statement discussed the conflicting data regarding de-escalation and duration of therapy [95]. Much of the difficulty in interpretation comes from the preponderance of observational study designs (that bias de-escalation towards better outcome as it tends to occur in patients who are already doing better) and the variable definitions of de-escalation used by investigators. Based upon the current data it seems that de-escalation and duration should be assessed separately, as they may have overlapping but unique roles in antimicrobial stewardship efforts.

BIOMARKER-BASED GUIDANCE FOR ANTIMICROBIAL TREATMENT

Procalcitonin has been the most extensively studied biomarker for use in the diagnosis of bacterial infections and guidance of antibiotic therapy. Procalcitonin is a short-lived hormone (precursor to calcitonin) that is rapidly induced by the inflammatory cytokines associated with bacterial infection. The short

half-life of procalcitonin and the correlation of its kinetics with the intensity of stimulus are desirable properties for any candidate biomarker to guide both the initiation and duration of antibiotic therapy in septic patients [96]. A comprehensive discussion on this topic can be found in the article by Gilbert et al in this Supplement [97], but we will highlight a few salient points with regard to antimicrobial duration.

Several large, multicenter trials have now been conducted in ICU populations: Procalcitonin to Reduce Antibiotic Treatments in Acutely Ill Patients (PRORATA) [98], Procalcitonin Guided Antibiotic Rational Decision Making in ICU Patients (ProGUARD) [99], and Stop Antibiotics on Procalcitonin Guidance Study (SAPS) [100]. In a meta-analysis of these 3 trials and 7 others, procalcitonin-guided patients had shorter antibiotic courses compared to controls, with no adverse impact on mortality or ICU length of stay [101]. However, a recent meta-analysis of 16 randomized controlled trials reported that decreased antibiotic utilization associated with procalcitonin-guided antibiotic discontinuation in critically ill patients represented low-certainty evidence with a high risk of bias and was primarily observed in studies without high protocol adherence and in those with algorithms combining procalcitonin and C-reactive protein [102]. The SSC guidelines [18] rank procalcitonin use to decrease antibiotic duration in sepsis as a weak recommendation with uncertain risk-benefit profile limiting its universal adoption for antibiotic discontinuation in sepsis across US hospitals and providers today.

CONCLUSIONS

The evidence regarding optimal antimicrobial treatment strategies for sepsis is conspicuously lacking and thus guideline recommendations remain necessarily vague despite universal acceptance of the importance of antibiotics. Unfortunately, retrospective and observational studies are significantly limited in their capacity to accurately capture the full treatment course of antimicrobials prescribed for sepsis (eg, outpatient administration of intravenous antibiotics, transfer to subacute rehabilitation centers to complete courses of therapy, and de-escalation to oral regimens), contributing to the incomplete data on this topic. There are a handful of on-going trials investigating treatment duration for some of the clinical syndromes associated with sepsis that are addressed here, but high-quality studies in this clinically heterogenous syndrome will remain difficult to conduct. Optimal antimicrobial duration in sepsis is likely to remain best determined through close collaboration between intensivists, infectious disease specialists, and other multidisciplinary providers in order to weigh the relative contributions of the many factors addressed in this review. Infectious disease consultation has been shown to improve patient outcomes in many studies of serious infections [103–106] and sepsis [107, 108], and this practice should be encouraged. Although we are unable to provide specific data-driven recommendations for duration of antibiotic therapy in sepsis, we hope that this narrative review will provide a call to action for conducting randomized control trials to specifically address the question of how long to treat in culture-positive and culture-negative sepsis.

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