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REVIEWS

Duration and Cessation of Antimicrobial Treatment

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Shortening the duration of antimicrobial therapy is an important strategy for optimizing patient care and reducing the spread of antimicrobial resistance. It is best used in the context of an overall approach to infection management that includes a focus on selecting the right initial drug and dosing regimen for empiric therapy, and de-escalation to a more narrowly focused drug regimen (or termination) based on subsequent culture results and clinical data. In addition to reducing resistance, other potential benefits of shorter antimicrobial courses include lowered antimicrobial costs, reduced risk of superinfections (including *Clostridium difficile*-associated diarrhea), reduced risk of antimicrobial-related organ toxicity, and improved drug compliance. There have been relatively few randomized clinical trials that study the optimal treatment durations for such serious infections as pneumonia (community- and healthcare/hospital-acquired), complicated intra-abdominal infection, and catheter-related bloodstream infection (CRBSI). Nonetheless, a growing number of studies have explored the possibilities of reducing the duration of antimicrobial therapy for at least certain patients with these infections, under certain circumstances. Professional organizations have compiled these data and used them to develop clinical practice guidelines to aid clinicians in choosing optimal treatment durations for individual patients. Many patients with hospital-acquired pneumonia, ventilator-associated pneumonia, or healthcare-associated pneumonia can be treated for 7-8 days, while 4-7 days and 14-day treatment durations may suffice for many patients with complicated intra-abdominal infections and uncomplicated CRBSI, respectively. This article first provides a general background on the rationale and data supporting shortened courses of antimicrobial therapy, before using 3 case studies to explore the practical implications of current knowledge and treatment guidelines when making decisions about treatment duration for individual patients with healthcare-associated pneumonia, complicated intra-abdominal infection, and CRBSI. *Journal of Hospital Medicine* 2012;7:S22–S33. © 2012 Society of Hospital Medicine

The appropriate duration of antimicrobial therapy for serious infections such as hospital- or healthcare-associated pneumonia, complicated intra-abdominal infection, and bacteremia has not been well studied. To the extent that guidelines for treatment duration exist, they are largely based on observational studies, clinical experience, and consensus, rather than data from well-designed clinical studies—although such studies and data are beginning to emerge, more so in some areas (pneumonia) than others (intra-abdominal infections and catheter-related bacteremia). Additional studies supporting treatment durations for these and other important infections are encouraged, given the widely recognized relationships between antimicrobial use and development of antimicrobial resistance, and between antimicrobial resistance and increased morbidity, mortality, and healthcare costs.[1–3] Duration is a component of antimicrobial exposure, and together with optimal dosing, has been linked with antimicrobial resistance and other adverse or unintended consequences of antimicrobial therapy. The general idea is to eradicate (kill) the pathogen as soon as possible, and then stop therapy, since ''dead bugs don't mutate.''

An overwhelming body of work has established a link between antimicrobial use and emergence of antimicrobial-resistant bacteria. This relationship holds for most, if not all, antimicrobial,[4–7] but appears to be particularly strong for broader-spectrum agents like fluoroquinolones,[8–14] extended-spectrum cephalosporins,[15–18] and carbapenems.[4,18–22] Using an antimicrobial from a particular drug class typically promotes development of resistance to all members of the class, but can also lead to more broad-based resistance including other drug classes, depending on the mechanisms of resistance. Emergence of resistance is expected to be especially high when a suboptimal antimicrobial regimen is administered for a prolonged time or duration,[7,23] as these conditions optimize pressure for selection of preexistent resistant strains or development of new ones.

Optimal efficacy and safety of antimicrobial therapy depends, first, on avoiding antimicrobials when they are not indicated, and second, when they are used, focusing on the 4 ''Ds'' of optimal antimicrobial therapy: right Drug, right Dose, De-escalation to pathogen-directed therapy, and right Duration of therapy.[24] Corresponding articles in this supplement have

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focused on the first 3 Ds: Dr Syndman on selection of the right drug and dose, and Dr Kaye on de-escalation of initial empiric therapy, when circumstances warrant it. The current article examines the rationale for reducing the duration of antimicrobial therapy (when possible), and current evidence or guidelines supporting the use of shorter courses of antimicrobial therapy for such infections as pneumonia (community-, hospital-, or healthcare-acquired/associated), complicated intra-abdominal infection, and bacteremia or sepsis. Key points will be illustrated through 3 case studies dealing with each of these general infection categories.

ADJUSTING DURATION TO OPTIMIZE ANTIMICROBIAL THERAPY

The ultimate goals of short-course antimicrobial therapy are to rapidly eradicate pathogenic microorganisms and reduce selective pressure for emergence of resistance. The primary potential advantages of shorter duration antimicrobial therapy include lower cost, less toxicity, better adherence, reduced antimicrobial resistance, and reduced disruption of endogenous flora and risk of ''superinfections,'' such as *Clostridium difficile*-associated disease.[23] Other potential benefits of shorter antimicrobial durations include a shorter length of hospital stay and (perhaps) earlier removal of an intravenous catheter, which would be expected to reduce risk of iatrogenic complications and facilitate early mobility and earlier return to full health. Effective short-course antimicrobial therapy also appears to better meet patient expectations of therapy than longer courses.[25]

Rapid or early eradication of pathogens depends not only on selecting an agent or combination of agents with activity against the causative pathogen, but also administering the agent in a manner that enables it to achieve its pharmacodynamic (PD) target for pathogen eradication in a rapid fashion.[23,26] The PD parameter that best predicts efficacy will vary for different antimicrobial classes, but the general idea is to use a dose, dosing schedule, and route of administration that rapidly achieves adequate tissue penetration and drug concentration at the infection site for a sufficient length of time for maximum efficacy. In brief, the general concept for short-course antimicrobial therapy is to ''hit hard and fast … then leave as soon as possible.''[23]

The World Health Organization (WHO) 2000 report on overcoming antimicrobial resistance also recognizes that ideal antimicrobial usage includes using the correct drug, administered by the best route, in the right amount, at optimal intervals, *for the appropriate period*, after an accurate diagnosis.[27] Administering antimicrobials for the wrong period of time (ie, duration) increases risk of resistance. In essence, the WHO report is another call to treat aggressively with shorter courses to help reduce antimicrobial resistance, and to avoid antimicrobial therapy when it is not warranted.

However, while there is general agreement about the utility of using as short an antimicrobial course as is consistent with efficacy, there has been a general dearth of information about exactly what the optimal duration is for particular agents (or drug classes) used to treat particular infections. This is especially the case for most infections occurring in critically ill patients in the hospital setting. Appropriate duration of therapy has been established for some infections, notably group A streptococcus pharyngitis, urinary tract infections, and some sexually transmitted diseases,[28–31] but treatment duration has not been firmly established for most serious infections. Furthermore, clinicians are often reluctant to shorten the duration of antimicrobial therapy in patients with serious infections for fear of incompletely eradicating the pathogen, thereby leading to relapses and significant morbidity or mortality.

Nevertheless, several studies have now been published that point to the effectiveness of ''shorter-course'' antimicrobial therapy for community-acquired pneumonia (CAP)[32–35] and hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP),[36–45] and a more limited number pointing to the effectiveness of shorter-course therapy for intra-abdominal infections[38,46,47] or bacteremia.[48–51] In addition, clinical practice guidelines recommend shorter-course antimicrobial therapy for most patients with CAP,[52] uncomplicated healthcare-associated pneumonia (HCAP) or HAP/VAP,[53] and complicated intra-abdominal infections[54]—and clinical practice guidelines for the management of intravascular catheter-related infection, including bacteremia, specify a standard duration of therapy and conditions under which a shorter (or longer) course may be considered.[55] Shorter-course therapy can be best implemented based on clinical parameters (eg, resolution of fever, reduction of leukocytosis) along with clinical judgment of the well-informed clinician with guidance from evidenced-based guidelines.

The remainder of this section will examine some of the preclinical and clinical evidence supporting shorter-course therapy for CAP. Subsequent sections of the article utilize 3 case studies to discuss current guidelines and supportive evidence for use of shorter-course antimicrobial therapy in patients with HCAP or HAP/VAP, complicated intra-abdominal infections, and bacteremia. The discussion of CAP is intended as an introduction that lays down some general concepts concerning shorter-duration therapy before delving into the serious hospital- or healthcare-related infections outlined above. Because there is more clinical research on duration of treatment for patients with HAP/VAP than for complicated intra-abdominal infections or bacteremia, the section on HCAP/HAP/VAP is much longer and detailed than the ones for complicated intra-abdominal infections or bacteremia.

CAP is defined as pneumonia developing in individuals who are not residents in a nursing home or extended-care facility, and who have not recently been hospitalized or had significant exposure to the healthcare setting. Pneumonia developing after 48 hours of hospital admission, and that was not incubating at the time of admission, is known as HAP,[53,56] and VAP is a subset of HAP, more precisely defined as HAP that arises after endotracheal intubation.[53] HCAP includes patients characterized by residence in a nursing home or extended-care facility or hospitalization for $\geq$2 days in the preceding 90 days or other significant exposure to the healthcare setting.[53,57,58]

DURATION OF THERAPY FOR CAP

A number of studies have reported similar efficacy with shortened versus longer durations of antimicrobial therapy for CAP.[33,59–64] Consistent with this, 2 recent meta-analyses of studies comparing shorter- versus longer-course therapy for mild-to-moderate CAP (22 randomized controlled trials and >8000 patients between them) reported similar efficacy and safety with shorter-course therapy.[65,66] In addition, other studies have reported an association between longer durations of antimicrobial therapy and development of resistance by community respiratory pathogens, especially when lower doses have been used.[67,68] These findings are consistent with the belief that prolonged treatment with a suboptimal antimicrobial regimen creates particularly fertile conditions for selection or development of antimicrobial-resistant strains.[65,66]

Data from preclinical studies provide a basis for understanding the effectiveness of shorter-dosing regimens of adequate antimicrobial therapy for CAP or other forms of pneumonia. In particular, in vitro time-kill studies[69–74] and animal models of infection[75–77] have demonstrated that *Streptococcus pneumoniae* can be rapidly eradicated without use of long-term therapy when appropriate antimicrobials are used. Consistent with these preclinical data, various clinical studies have also shown that *S pneumoniae* and other respiratory pathogens are rapidly eradicated from lower respiratory tract secretions after initiation of appropriate antimicrobial treatment. For example, Montravers et al. reported that 94% of respiratory pathogens were eradicated from the lungs of 76 patients with VAP after just 3 days of antimicrobial therapy.[78]

Based on the available data, the 2007 Infectious Diseases Society of America (IDSA)/America Thoracic Society (ATS) guidelines for CAP management recommend a minimum of 5 days of antimicrobial treatment, while noting that most patients become clinically stable within 3-7 days of treatment onset and rarely require longer durations.[52] The guidelines further recommend that CAP patients should be afebrile for 48–72 hours and should have no more than 1 CAP-associated sign of clinical instability before discontinuation of therapy. Although the general movement is toward use of shorter-duration treatment courses than the traditional 7–10 days or longer, the IDSA/ATS guidelines acknowledge that longer durations may be needed in certain situations.[79]

CASE 1: HEALTHCARE-ASSOCIATED PNEUMONIA

Case 1 is a 72-year-old woman admitted with findings consistent with HCAP who was initiated on an empiric therapy regimen of vancomycin and piperacillin-tazobactam. Results from blood and sputum cultures obtained prior to treatment initiation came back on day 3, and were negative for pathogenic bacteria. White blood cell (WBC) counts were trending downward, and the patient appeared to be stabilizing. She still had an elevated WBC count, slight fever (temperature maximum of 101.4°F for the past 24 hours), and lung crackles at the right lung base. Because Gram stain failed to identify Gram-positive cocci clusters, and there was no culture evidence of methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*, vancomycin treatment was terminated and the patient was switched to single-agent therapy with intravenous ceftriaxone, a nonpseudomonal third-generation cephalosporin. On hospital day 5, there was continuing evidence of response to antimicrobial therapy. The patient reported feeling better and she was breathing comfortably. Her cough was much improved, sputum production was markedly decreased, and her fever had resolved. Now, on day 7, the patient is still afebrile, her WBC count is normal, and she has 96% oxygen saturation on room air.

The question before the clinician is whether to terminate or continue antimicrobial therapy, and if continued, with what regimen and for how long? In addition, if a decision is made to continue antimicrobial therapy, there is a possibility of switching from an intravenous to oral treatment regimen. An examination of the literature and current treatment guidelines for HCAP/HAP/VAP should enable a more informed decision, one that optimally benefits not only this patient, but all subsequent ones who might be exposed and infected with a resistant pathogen that develops when treatment is continued longer than necessary.

Using Clinical Parameters to Shorten Antimicrobial Therapy

A prospective study by Dennesen et al., published 10 years ago, was one of the first suggesting the possibility of shortened duration of antimicrobial therapy for VAP.[80] At the time, duration of antimicrobial therapy for VAP typically ranged from 7 to 21 days, and was most commonly 14 to 21 days. In this study, Dennesen and coworkers examined symptom resolution in 27 patients diagnosed with VAP based on clinical, radiologic, and microbiological criteria, each of whom received appropriate antimicrobial therapy based on culture susceptibility data.[80] Significant improvements

were observed for all clinical parameters examined (highest temperature, leukocyte count, pressure of arterial oxygen to fractional inspired oxygen [Pa_{O2}/FI_{O2}] ratio, semiquantitative culture result of endotracheal aspirate), usually first appearing within the first 6 days of antimicrobial therapy. Furthermore, analyses of specific pathogens showed that appropriate antimicrobial therapy rapidly eradicated endotracheal colonization with *S pneumoniae*, *Haemophilus influenzae*, and *S aureus*, but not of *P aeruginosa* or Enterobacteriaceae. Moreover, endotracheal colonization with resistant pathogens tended to occur when antimicrobial therapy was continued beyond the first week. Taken together, these results suggested that prolonged antimicrobials beyond 7 days usually did not benefit VAP patients, and in fact increased risk of superinfection with a resistant strain. However, it is important to make a distinction between VAP and, for example, skin or bloodstream infections involving *S aureus*. While improved signs and symptoms generally indicate clinical cure for VAP, this reasoning should not be applied to *S aureus* bacteremia.

The findings from Dennesen et al. are generally consistent with those from Montravers et al., which showed that 94% of respiratory pathogens were eradicated from the lungs of VAP patients 3 days after initiation of antimicrobial therapy.[78] They are also consistent with the findings from a 2005 study by Vidaur et al., which demonstrated resolution of fever (<38°C), Pa_{O2}/FI_{O2} (>250 mmHg), and WBC/leukocyte count (<10,000) in 73%, 75%, and 53% of VAP patients, respectively, without acute respiratory distress syndrome (ARDS; n = 75) after 3 days of appropriate antimicrobial therapy.[81] However, Vidaur et al. reported that fever took roughly twice as long to resolve in VAP patients with ARDS (n = 20) versus without ARDS, and that hypoxia resolution was less useful when evaluating treatment response in ARDS patients. As with the Dennesen et al. study,[80] the results from Vidaur et al. suggest that measures of core body temperature and oxygenation can be useful guides for clinicians in determining whether to shorten the duration of antimicrobial therapy for patients with VAP, HAP, or HCAP.[81]

Along the same lines, the clinical pulmonary infection score (CPIS) has established itself as a means for the early termination (shortening) of initial empiric antimicrobial therapy in particular VAP patients. The CPIS is derived by scoring 5–7 clinical indices relevant for the diagnosis of VAP, as illustrated in Table 1.[82] A score of >6 is considered suggestive of pneumonia, while one ≤6 implies low likelihood of pneumonia. A 2000 study by Singh et al. randomized 81 consecutive patients with pulmonary infiltrates and a CPIS ≤6 to receive either standard antimicrobial therapy (at discretion of the clinician) or ciprofloxacin monotherapy, with the intention of reevaluating patients at day 3.[45] For patients in the ciprofloxacin (experimental) group, antimicrobial therapy was terminated at day 3 if the CPIS remained ≤6. As a result, only 28% of patients in the experimental group had antimicrobial therapy continued beyond day 3, compared with 90% of patients in the standard therapy group ($P = 0.0001$). More importantly, there were no significant differences in mortality between patients in the 2 treatment groups, despite a significantly shorter treatment duration for those in the experimental group (3.0 vs 9.8 days, $P = 0.0001$). In addition, mean length of intensive care unit (ICU) stay was significantly shorter (9.4 vs 14.7 days, $P= 0.04$) and mean antimicrobial cost was significantly lower ($259 vs $640, $P = 0.0001$) for patients in the experimental versus standard therapy group.

Furthermore, a significantly greater proportion of patients in the standard versus experimental therapy group exhibited evidence of antimicrobial resistance or superinfections (38% vs 14%, $P = 0.017$). The 2005 clinical practice guidelines for HAP, VAP, or HCAP state, "A modified CPIS of 6 or less for 3 days, proposed by Singh and coworkers, is an objective criterion to select patients at low risk for early discontinuation of empiric treatment of HAP."[53] While the Singh et al. study provides the rationale for shorter-course therapy in ICU patients with pulmonary infiltrates who have low likelihood of pneumonia (CPIS ≤6), this criterion may or may not pertain to "HAP/VAP" more strictly, and still requires validation in

TABLE 1. Clinical Pulmonary Infection Score (CPIS) for the Diagnosis of VAP

	Points
Temperature °C	
≥36.5 and ≤38.4	0
≥38.5 and ≤38.9	1
≥39 or ≤36.0	2
Tracheal secretions	
Absence of secretions	0
Presence of non-purulent secretions	1
Presence of purulent secretions	2
Pulmonary radiography (chest X-ray)	
No infiltrate	0
Diffused (or patchy) infiltrate	1
Localized infiltrate	2
WBCs, leukocytes/mm^{-3}	
≥4000 and ≤11,000	0
<4000 or >11,000	1
+Band forms ≥500	2
Oxygenation: Pa_{02}/FI_{02} mmHg	
>240 or ARDS	0
≤240 and no evidence of ARDS	2
Culture of tracheal aspirate (semiquantitative: 0–1–2 or 3+)	
Pathogenic bacteria cultured ≤1+ or no growth	0
Pathogenic bacteria cultured >1+	1
+ same pathogenic bacteria seen on the gram stain >1+	2
Progression of pulmonary infiltrate	
No radiographic progression	0
Radiographic progression (ARDS excluded)	2

NOTE: Adapted from Pugin et al.[82] and Singh et al.[45] Total points = CPIS; an initial score is based upon the first 5 variables. The last 2 variables are assessed on day 2 or 3. A score of >6 is suggestive of pneumonia.
Abbreviations: ARDS, acute respiratory distress syndrome; Pa_{02}/FI_{02}, pressure of arterial oxygen to fractional inspired oxygen; VAP, ventilator-associated pneumonia; WBC, white blood cell.

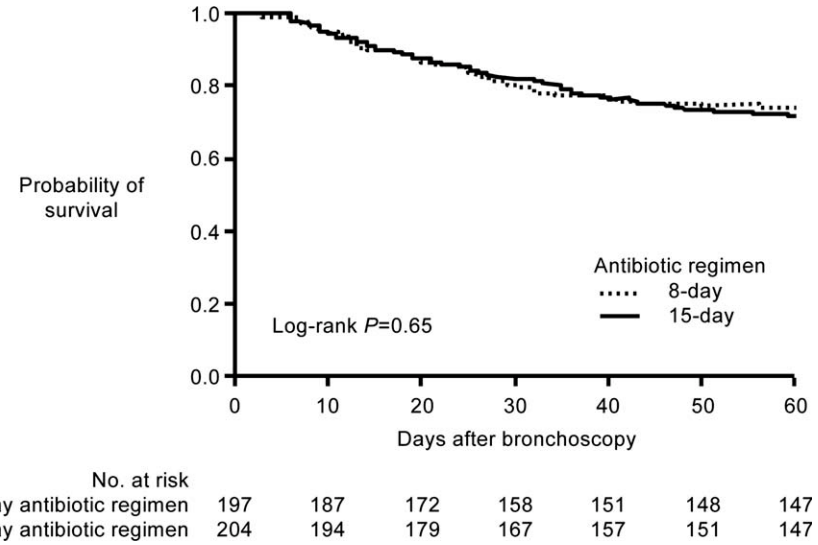

FIG. 1. Kaplan-Meier estimates of the probability of survival. (Reproduced from Chastre et al.[37])

patients with more severe forms of VAP. Incidentally, although the CPIS was designed to define VAP, and there are no data validating its use for other types of pneumonia, the clinical experience by this author indicates that it can be helpful in evaluating HCAP and non-VAP HAP as well.

Clinical Trial to Support Shortened Duration of HCAP/HAP/VAP Therapy

A French study published in *JAMA* in 2003 provides more direct support that approximately 1 week of antimicrobial therapy produces effectiveness comparable to more traditional 2–3-week therapy for most patients with VAP.[37] In this prospective, multicenter, randomized, double-blind (until day 8) clinical trial, 401 patients with microbiologically proven VAP were randomly assigned to receive either 8 days (n = 197) or 15 days (n = 204) of initial empiric antimicrobial therapy selected by the treating physician. No significant differences were observed between the 8-day and 15-day treatment groups for the 2 primary efficacy endpoints of death from any cause (18.8% vs 17.2%) and microbiologically documented pulmonary infection recurrence (28.9% vs 26.0%). There were also no differences between the groups for number of mechanical ventilation-free days (8.7 vs 9.1 days), number of organ-failure-free days (8.7 vs 8.9 days), length of ICU stay (30.0 vs 27.5 days), unfavorable outcome (death, pulmonary infection recurrence, or prescription of a new antimicrobial) (46.2% vs 43.6%), mortality rate on day 60 (25.4% vs 27.9%), or in-hospital mortality (32% vs 29.9%).

Conversely, patients in the 8-day treatment group had significantly more antimicrobial-free days (13.1 vs 8.7 days, $P < 0.001$), and among patients who developed recurrent infections, multidrug-resistant pathogens emerged more frequently in patients in the 15-day versus 8-day treatment group (62.0% vs 42.1%, $P = 0.04$). However, there was an apparent exception to the general comparable efficacy of the 8- and 15-day treatment regimens for infections caused by nonfermenting Gram-negative bacilli, including *P aeruginosa*. For primary infections caused by nonfermenting Gram-negative bacilli, the 8-day versus 15-day regimen was associated with higher rates of pulmonary recurrence (40.6% vs 25.4%). Interestingly, the 8-day regimen was not associated with more adverse outcomes here, just a higher recurrence rate. With respect to primary infections caused by MRSA, no differences were observed between the 2 treatment regimens for death for all causes (23.4% vs 30.2%) or pulmonary infection recurrence (33.3% vs 42.9%). Figure 1 presents the probability of survival data for the 8-day and 15-day treatment groups.

Hence, the data from the Chastre et al. study[37] support use of an 8-day (or shortened) regimen as standard antimicrobial therapy for most patients with VAP, with some possible exceptions. Additional studies provide further support for this general conclusion. For example, a prospective, randomized, controlled trial by Micek et al. evaluated the impact of using an antimicrobial discontinuation policy based on clinical criteria (discontinuation group; n = 150)—versus the decision of treating physicians (conventional group, n = 140)—to determine the duration of antimicrobial therapy for VAP, and observed a statistically shorter treatment duration in the discontinuation versus conventional management group (6.0 vs 8.0 days, $P = 0.001$), but no difference between the groups for hospital mortality (32.0% vs 37.1%), ICU length of stay (6.8 vs 7.0 days), or VAP recurrence (17.3% vs 19.3%).[42] A prior study by the same group reported a shorter duration of antimicrobial therapy for VAP following implementation of an antimicrobial guideline (vs prior to implementation) (8.6 vs 14.8 days, $P < 0.001$), and a lower rate of VAP recurrence among

TABLE 2. VAP in All Patients According to Treatment Duration

Patient Characteristic	≤ 8 Days (n = 98)	≥ 9 Days (n = 354)	*P* Value
Mean antimicrobial days	6.2	16.8	0.0001
Mean APACHE II	18	20	0.0009
% Trauma	71	68	0.63
Mean time to onset, days	17.7	17.8	0.97
Recurrence	11%	25%	0.004
Death	13%	11%	0.59
Nonfermenting Gram-negative bacilli recurrence	22% (n = 27)	34% (n = 127)	0.27
Staphylococcus aureus recurrence	20% (n = 10)	38% (n = 47)	0.47

NOTE: Adapted from Hedrick et al.[39]
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; VAP, ventilator-associated pneumonia.

patients in the "after" period (7.7% vs 24.0%, $P = 0.03$). However, interpretation of the results was complicated by the fact that initial empiric therapy was more often appropriate during the "after" versus "before" guideline implementation period (94.2% vs 48.0%, $P < 0.001$).[40]

A limited number of studies have focused further on shortened duration of therapy for patients with VAP caused by Gram-negative bacteria, and particularly by nonfermenting Gram-negative bacilli. A retrospective study by Hedrick et al. analyzed the relationship between antimicrobial duration and outcomes of 452 episodes of VAP in the ICU, 154 caused by nonfermenting Gram-negative bacilli.[39] In the study, 127 patients infected with a nonfermenting Gram-negative bacillus received ≥9 days (mean 17.1 ± 0.7 days) of antimicrobial therapy, while 27 received 3-8 days (mean 6.4 ± 0.3 days) of therapy. No significant differences were observed between the shorter- and longer-duration groups for mortality (22% vs 14%, $P = 0.38$) or VAP recurrence (22% vs 34%, $P = 0.27$) for these patient populations. Table 2 provides the results for all 452 VAP episodes based on ≤8 days or ≥9 days of antimicrobial therapy.

The retrospective nature of the study limits the ability to more confidently interpret the results, but the data appear to be consistent with the conclusion that short-duration therapy does not necessarily increase recurrence or worsen other outcomes in patients with VAP caused by nonfermenting Gram-negative bacilli. The most common Gram-negative bacilli associated with VAP in the study were *P aeruginosa* (18% of all infections), *Enterobacter cloacae* (11%), *Acinetobacter* spp (11%), *Klebsiella pneumoniae* (7%), *Stenotrophomonas maltophilia* (7%), *Serratia* spp (7%), *H influenzae* (6%), and *Escherichia coli* (4%). In addition, the study results suggest that short-duration therapy is at least as effective as longer-duration therapy for the overall VAP population, with potential benefits in terms of reduced antimicrobial use and lower rate of recurrence.

Another recent retrospective analysis examining an even shorter course of antimicrobial therapy (5 days) for patients with HAP associated with Gram-negative bacteria reported a low overall recurrence rate (14%) and a critical care mortality rate (34.2%) in line with prior studies of short-term therapy for VAP/HAP.[44] However, the HAP relapse rate was significantly higher in patients with HAP caused by nonfermenting Gram-negative bacilli versus other Gram-negative species (17% vs 2%, $P = 0.03$).

A recent US pilot study explored the use of repeat bronchoalveolar lavage (BAL) to guide antimicrobial duration in 52 patients with VAP, and compared the results with a matched control group of 52 VAP patients treated before institution of the BAL pathway.[43] Antimicrobial therapy in the pathway patients was discontinued if pathogen growth was <10,000 colony forming units/mL on the repeat BAL performed on day 4 of therapy. One objective was to determine whether a repeat BAL strategy, such as the one here, might be able to identify patients with VAP due to nonfermenting Gram-negative bacilli or other microorganisms who could be safely and effectively treated with shorter-duration therapy.

Results showed that the antimicrobial duration was significantly shorter for patients in the pathway group than the matched control group (9.8 vs 3.8 days, $P < 0.001$), including the subset of patients with VAP associated with nonfermenting Gram-negative bacilli (10.7 vs 14.4 days, $P < 0.001$). No significant differences were observed between the overall treatment populations for VAP recurrence, mechanical ventilator-free ICU days, ICU-free hospital days, or mortality. Repeat BAL showed most VAP isolates in the study group (83%) responded to initial therapy with a mean duration of 8.8 days. Nonresponders without concomitant infections received significantly longer treatment than pure responding isolates (14.4 vs 7.3 days, $P < 0.001$), and the most common nonresponding microorganisms were *P aeruginosa* (41% response rate) and *S maltophilia* (50% response rate), 2 nonfermenting Gram-negative bacilli.

Most nonfermenting Gram-negative bacilli-associated VAP isolates in the study group did respond on repeat BAL (59%). These responders were treated for a mean duration of 8.2 days, and exhibited a similar recurrence rate versus that observed for the matched control group (12.0% vs 17.9%, $P = 0.71$). These pilot study results suggest that repeat BAL might be used to identify patients likely to benefit from short-duration therapy, including patients infected with nonfermenting Gram-negative bacilli. Further study on this is needed.

ATS/IDSA Guidelines for Duration of HCAP/HAP/VAP Therapy

Based largely on the studies by Dennesen et al.[80] and Luna et al.[83] indicating most VAP patients who

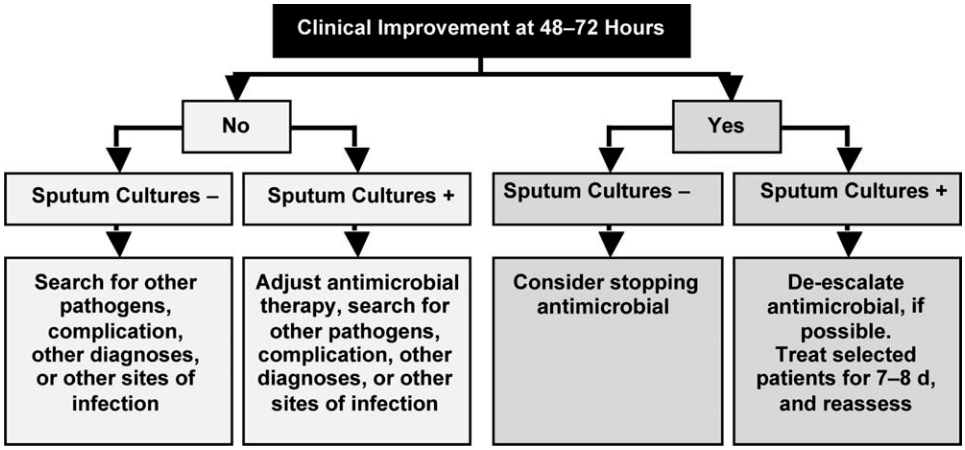

FIG. 2. Summary of management strategies for patients with suspected healthcare-associated pneumonia, hospital-acquired pneumonia, or ventilator-associated pneumonia, 48 to 72 hours after initiation of empiric antimicrobial therapy. (Reprinted with permission of the American Thoracic Society. Copyright© American Thoracic Society. 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. Official Journal of the American Thoracic Society.)

respond to appropriate antimicrobial therapy do so within the first 6 days, and those by Chastre et al.[37] and Singh et al.[45] pointing to the efficacy and safety of shorter-duration VAP therapy, the 2005 ATS/IDSA guidelines recommend the use of shorter-duration antimicrobial therapy for most patients with HCAP or HAP/VAP.[53] More specifically, the guidelines state, "If patients receive an initially appropriate antimicrobial regimen, efforts should be made to shorten the duration of therapy from the traditional 14 to 21 days to periods as short as 7 days, provided that the etiologic pathogen is not *P. aeruginosa*, and that the patient has a good clinical response with resolution of clinical features of infection."[53] Figure 2 presents an overview of the ATS/IDSA guidelines for HCAP/HAP/VAP management 48 to 72 hours after initiation of empiric antimicrobial therapy.[53]

Note that the clinician should consider terminating antimicrobial therapy in patients with clinical improvement and negative cultures or other evidence suggestive of a noninfectious cause. CPIS can also be helpful when deciding whether to terminate initial empiric therapy in a patient with clinical improvement after 2–3 days of therapy and negative cultures. If cultures are positive, the clinician should consider whether antimicrobial de-escalation is possible (as discussed by Dr Kaye in the corresponding supplement article), and aim to treat selected patients with an antimicrobial course lasting 7–8 days. After 7–8 days, patients should be reassessed for treatment termination or other appropriate actions.

The ATS/IDSA guidelines also provide recommendations for route of drug administration, and if and when to switch from an intravenous to oral agent. In particular, the guidelines state that all patients with HCAP, HAP, or VAP should initially receive therapy intravenously, but conversion to oral/enteral therapy may be possible in certain responding patients, ie, those with a good clinical response and a functioning intestinal tract.[53] Fluoroquinolones and linezolid have oral formulations with bioavailability equivalent to the intravenous form, meaning the oral formulations are capable of achieving high levels at the site of infection. This may facilitate conversion to oral therapy in select patients. Early step-down is safe and effective with fluoroquinolones.[84,85]

Based on the information just reviewed, the antimicrobial can be terminated on day 7 for case 1. She is afebrile, and her WBC and oxygenation are normal. In fact, since her records show she was responding at day 5, consideration could have been given to switching from intravenous to oral therapy at that time, and perhaps even discharging her to the rehabilitation center.

CASE 2: INTRA-ABDOMINAL INFECTION (DIVERTICULITIS)

Case 2 is a 56-year-old woman who presents with sepsis and diverticular abscess with walled-off perforation. Upon hospital arrival, Interventional Radiology inserted a drain, and the patient was initiated on ciprofloxacin and metronidazole therapy. Day 3 examination showed improvement in WBC count and normal vital signs, but the patient still had a low-grade fever (100.9°F). Abdominal examination results were improved, but with some diffuse tenderness. Initial cultures of the abdominal abscess isolated Gram-negative rods, and the patient was continued on ciprofloxacin/metronidazole. Further cultures on day 4 identified an extended-spectrum β-lactamase (ESBL)-producing *E coli* organism as the causative pathogen. The patient was switched from ciprofloxacin/metronidazole to ertapenem. It is now hospital day 8, and the patient continues to show good response to treatment. She is afebrile and WBC count is normal. The abscess catheter is no longer draining. Her abdominal pain is improved, and she is complaining that she is hungry. A repeat computed tomography scan shows resolution

of the abscess and no evidence of bowel perforation. Should antimicrobial therapy be continued in this patient, and if so, with what agent and for how long?

Guidelines from the Surgical Infection Society and IDSA state that antimicrobial therapy of established or complicated intra-abdominal infection in adults "should be limited to 4–7 days, unless it is difficult to achieve adequate source control."[54] This is because extended antimicrobial exposure increases antimicrobial cost and risk of resistance, superinfection, *C difficile*-associated colitis, or other untoward and unintended consequences of antimicrobial therapy, and there is no evidence that longer treatment durations improve outcomes.[46,47,54,86] Runyon et al. randomized 90 patients with spontaneous bacterial peritonitis or culture-negative neutrocytic ascites to receive 5 days or 10 days of cefotaxime monotherapy, and reported similar rates of infection-related mortality (0% vs 4.3%), hospitalization mortality (33% vs 43%), bacteriologic cure (93% vs 92%), and recurrence of ascitic fluid infection (12% vs 13%).[46] Furthermore, shorter-course therapy was associated with significantly lower antimicrobial administration and costs. Similarly, a recent prospective, randomized, double-blind trial comparing 3 versus $\geq$5 days of ertapenem therapy in 111 patients with community-acquired intra-abdominal infection reported similar cure (93% vs 90%) and eradication rates (95% vs 94%).[86] However, it should be noted that the mean duration of antimicrobial therapy in the longer-duration group was still relatively short (5.7 days, range of 5-10 days).

Studies also indicate there is a very low risk of infection recurrence or treatment failure when antimicrobial therapy is terminated in a patient diagnosed with a complicated intra-abdominal infection who no longer shows signs of continuing infection.[38,87] Lennard et al. compared postoperative outcomes in 65 patients with or without leukocytosis and fever at the conclusion of antimicrobial therapy for intra-abdominal sepsis, and reported development of intra-abdominal infection in 7 of 21 (33%) with persistent leukocytosis.[87] None of the 30 patients with normal WBC counts at the end of therapy developed an intra-abdominal infection postoperatively. Furthermore, intra-abdominal infection occurred postoperatively in 11 of 14 patients (79%) who responded to treatment but were still febrile at the time of antimicrobial discontinuation.

Similar results were obtained in a much larger, more recent study that retrospectively analyzed the relationship between duration of antimicrobial therapy and infectious complications for patients with intra-abdominal infections.[38] In the study, 929 patients with intra-abdominal infections associated with either fever or leukocytosis were organized into 4 quartiles based on total duration of antimicrobial therapy (quartile 1: 0–7 days, n = 218; quartile 2: 8–12 days, n = 217; quartile 3: 13–17 days, n = 246; and quartile 4: >17 days, n = 248) or antimicrobial duration after resolution of leukocytosis (quartile 1: 0–5 days, n = 130; quartile 2: 6–10 days, n = 127; quartile 3: 11–15 days, n = 124; and quartile 4: >15 days, n = 118). Based on either total duration of antimicrobial therapy or duration after leukocytosis resolution, risk of recurrence was significantly higher for patients in quartiles 3 or 4 versus those in quartile 1, and there was no difference between quartiles 1 and 2.

Taken together, these results suggest that antimicrobial therapy for intra-abdominal sepsis can be shortened in patients exhibiting a clinical response to treatment, if there are no signs of persistent leukocytosis or fever. Hence, clinicians should use the resolution of clinical signs of infection as a guide to determine when during the 4–7-day window antimicrobial therapy should be terminated.[54] In practical terms, this usually means treatment can be terminated when the patient is afebrile, has normal WBC counts, and is able to tolerate an oral diet.

Based on the clinical status of case 2 after 8 days of antimicrobial therapy (afebrile with normal WBC counts and requesting oral diet), the ertapenem regimen should be stopped. There is no reason to consider further outpatient antimicrobial therapy for this particular patient, but the Surgical Infection Society and IDSA guidelines discuss the type of patient who should be considered for oral or outpatient antimicrobial therapy. According to the guidelines, the patient convalescing from a complicated intra-abdominal infection may receive oral antimicrobial therapy, but that therapy should only be included as a component within the brief treatment duration already mentioned, ie, in total, it should rarely exceed 7 days.[54] Such therapy is rarely indicated for patients who are afebrile, with normal peripheral WBC/leukocyte counts, and with return of bowel function. These recommendations make it clear that no further antimicrobial therapy is warranted for case 2.

However, for appropriate patients who are recovering from a complicated intra-abdominal infection and are able to tolerate an oral diet, an oral antimicrobial regimen selected on the basis of identified primary isolates may be used for completion of therapy.[54] In the absence of cultures, an oral regimen that covers commonly isolated pathogens (eg, *E coli*, streptococci, and *Bacteroides fragilis*) should be considered. Common regimens include an oral cephalosporin or fluoroquinolone with metronidazole, or amoxicillin-clavulanic acid, assuming susceptibility studies do not demonstrate resistance. Given the identification of an ESBL-producing *E coli* for case 2—a pathogen relatively resistant to oral antimicrobial—an oral regimen probably would not have been viable for this patient even earlier in the treatment course. Lastly, a repeat computed tomography scan was used for the case here. It should be noted that there are currently no well-established criteria for determining when repeat imaging is needed to confirm resolution of fluid collections. This

should be a clinical decision. A general practice is that the catheter is left in place until there is minimal drainage (eg, <10 mL/day); catheter sinograms can also be helpful in determining the status of the abscess.

CASE 3: CENTRAL LINE-ASSOCIATED BACTEREMIA

Case 3 is a 56-year-old man with status epilepticus, intubation, and ICU stay. He was initially treated with vancomycin and piperacillin-tazobactam for a fever of 103.4°F on day 5 of hospitalization. Blood cultures grew Gram-positive cocci. The central venous catheter was removed, and the initial antimicrobial regimen was de-escalated to vancomycin monotherapy, which was associated with continued improvement in fever and WBC count, and clinical stability on hospital day 7. At that time, further blood culture analyses isolated methicillin-susceptible *S aureus* (MSSA), and the antimicrobial regimen was switched/de-escalated from vancomycin to cefazolin. It is now hospital day 9 (day 3 of cefazolin) and the patient continues to respond and is afebrile. Repeat blood cultures show no bacterial growth, and a transesophageal echocardiograph (TEE) was performed and revealed normal heart valves. Should the antimicrobial therapy be continued for this patient, and if so, with what agent and for how long?

The IDSA guidelines for management of intravascular catheter-related infections recommend catheter removal and 4–6 weeks of antimicrobial therapy for patients with *S aureus* catheter-related bloodstream infection (CRBSI), unless the patient has exceptions allowing consideration of shorter-duration therapy (minimum of 14 days, with day 1 being the first day of negative blood culture results).[55] These exceptions include absence of diabetes; immunocompetence (no immunosuppression); removal of the infected catheter; no prosthetic intravascular device (eg, pacemaker or recently placed vascular graft); no evidence of endocarditis or suppurative thrombophlebitis on TEE and ultrasound, respectively; fever and bacteremia resolved within 72 hours after initiation of appropriate antimicrobial therapy; and no evidence of metastatic infection on physical examination and sign- or symptom-directed diagnostic tests.

Short-duration (10-16 day) antimicrobial therapy has been reported to yield similarly low recurrence or relapse rates as longer courses of therapy in patients with uncomplicated catheter-associated *S aureus* bacteremia.[50,51,88,89] A small 1989 study by Ehni and Reller prospectively followed 13 patients with *S aureus* CRBSI who had received short-course therapy (<17 days), and reported only 1 case of relapse with endocarditis (8% relapse rate).[50] A subsequent study by Malanoski et al. retrospectively analyzed the data from 55 patients with *S aureus* CRBSI.[51] Excluding the 8 patients with early complications, the authors observed similar rates of relapse in patients treated for 10–15 days and those receiving longer courses of antimicrobial therapy (0% vs 4.7%). The clinical characteristics of the 2 treatment duration groups were similar, and delayed catheter removal was linked with persistence of bacteremia ($P = 0.01$).

A more recent multicenter, prospective observational study by Chang et al. examined recurrence and the impact of antimicrobial treatment in 505 consecutive patients with *S aureus* bacteremia, and determined that duration of antimicrobial therapy was not a factor associated with relapse.[88] This was true both for patients with bacteremia resulting from endocarditis, bacteremia with no apparent source, or bacteremia due to a focus that could not be cured or removed (≥28 days therapy after defervescence, ≥28 days therapy, or <28 days therapy), or those with bacteremia resulting from a source amenable to definitive cure, such as an intravascular device that could be removed, an abscess that could be incised and drained, or an infected bone that could be resected (>14 days, 10–14 days, or <10 days therapy). Similarly, a 2005 prospective study by Thomas and Morris determined there was no relationship between treatment duration (≤7 vs ≥8 days, ≤10 vs ≥10 days, or ≤14 vs ≥15 days; $P = 0.62$, 0.87, and 0.16, respectively) and rate of relapse for 276 patients with cannula-associated *S aureus* bacteremia.[89] Longer-duration antimicrobial therapy is warranted in patients with CRBSI and an early complicated course, eg, fever and/or bacteremia persisting for >3 days after catheter removal.[90]

According to the IDSA guidelines, a TEE should be obtained for all patients with CRBSI involving *S aureus* who are being considered for a shorter duration of therapy, and the TEE should be performed at least 5–7 days after onset of bacteremia to minimize risk of false-negative results.[55] High rates of infective endocarditis are observed in patients with *S aureus* bacteremia,[89,91–93] with higher rates in patients with MSSA versus MRSA bacteremia (43.4% vs 19.6%, $P < 0.009$).[91] TEE is essential to diagnose endocarditis and detect other complications of bacteremia.[92,93] This recommendation for use of TEE does not necessarily apply to all patients with CRBSI when *S aureus* is not involved.

Figure 3 summarizes the general recommendations from the IDSA guidelines for the management of CRBSI in patients with a short-term catheter.[55] The figure illustrates the varied recommendations for treatment duration depending on whether the infection is complicated or uncomplicated, and based on the pathogenic microorganism. Returning to case 3, the patient meets the general criteria for shorter duration of antimicrobial therapy: he is not diabetic or immunosuppressed, his catheter has been removed, he does not have any prosthetic intravascular devices, his fever and bacteremia (based on blood cultures) resolved within 3 days of initiating cefazolin therapy, and there

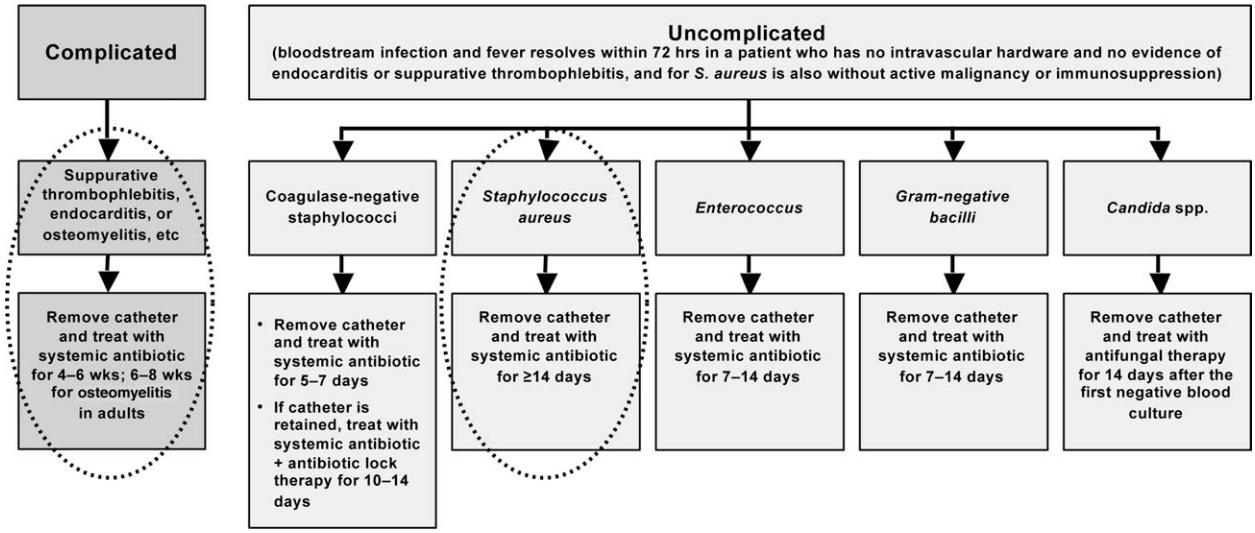

FIG. 3. Recommendations from the 2009 Infectious Diseases Society of America guidelines for the management of catheter-related bloodstream infection in patients with a short-term catheter. (Reproduced from Mermel et al.[55])

is no evidence of endocarditis or other complications of bacteremia. Hence, he is an excellent example of a patient with uncomplicated MSSA CRBSI who meets the criteria for consideration of shortened antimicrobial therapy. Based on the clinical practice guidelines, the patient should continue on intravenous cefazolin for a 14-day course of therapy, at which time he can be re-evaluated. A recent review of bloodstream infections caused by various pathogens similarly concluded that the minimum treatment duration for low-risk patients with *S aureus* CRBSI is 14 days.[48] As a final point, it is also important to note that there is no role for oral therapy in patients with CRBSI, so whether shortened or not, the chosen regimen should be administered intravenously.

CONCLUSIONS

Shortening the duration of appropriate and adequate antimicrobial therapy represents one strategy for reducing pressure for selection or development of resistant pathogenic microorganisms. Other potential benefits of shorter courses of antimicrobial therapy include reduced risk of antimicrobial-associated infections (superinfection, *C difficile*-associated diarrhea) and other antimicrobial-related adverse events, improved compliance, and reduced antimicrobial costs. Clinicians are sometimes concerned that reducing antimicrobial courses for patients with serious infections, such as HCAP/HAP/VAP, complicated intra-abdominal infection, and CRBSI, will lead to incomplete eradication of pathogenic microorganisms, leading to disease recurrence and increased morbidity and mortality. When managing patients with these serious infections, clinicians often turn to the literature and recommendations from professional organizations for guidance. Available data from randomized controlled and nonrandomized clinical trials indicate that shorter-course therapy is effective and safe for patients with CAP, HCAP/HAP/VAP, complicated intra-abdominal infections, and CRBSI. Based on these data, and consensus/expert opinion, clinical practice guidelines have been developed that recommend specific durations of antimicrobial therapy for each of these infections.

Although greater study of antimicrobial therapy duration is needed, the current and developing literature and current treatment guidelines should enable clinicians to recognize patients who would benefit from shortened courses of antimicrobial therapy. In doing so, they would help to lower antimicrobial costs and reduce the growing problem of antimicrobial resistance, with its wide-ranging, negative consequences for current and future patients, and the clinicians who treat them.

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