Use of Broad-Spectrum Antimicrobials for the Treatment of Pneumonia in Seriously Ill Patients: Maximizing Clinical Outcomes and Minimizing Selection of Resistant Organisms

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Among various risk factors for death among critically ill patients with serious infection, inappropriate antimicrobial therapy is an important factor that clinicians can modify directly. The presence of multidrug-resistant bacteria is the primary reason that patients with ventilator-associated pneumonia receive inappropriate antimicrobial therapy. Empirical antimicrobial therapy for ventilator-associated pneumonia should be initiated promptly and should have a broad spectrum that covers all potential antimicrobial-resistant pathogens. Delaying the start of therapy or modifying an inappropriate antimicrobial regimen does not improve outcome, probably because the change comes too late to redirect the course of illness. Timely empirical therapy with highly effective agents that are rapidly bactericidal could minimize the emergence of resistance. Broad-spectrum therapy should be streamlined (i.e., de-escalated), as appropriate, on the basis of microbiological data and clinical response. Switching to narrower-spectrum therapy that is directed by culture results may minimize the emergence of resistance. For some patients, clinical response will allow a shortening of the duration of antimicrobial therapy.

RESISTANCE PROMOTED BY ANTIMICROBIAL USE

Although much attention has been focused on the emergence of antimicrobial-resistant organisms in hospitals, the genesis of antimicrobial resistance is often in outpatients. The manner in which antimicrobial agents are used in nonhospital settings has a great bearing on the microbial environment for critically ill patients. Results from the National Laboratory Medical Care Survey show that the use of broad-spectrum antimicrobial agents for adults has increased significantly (from 24% of all antimicrobials in 1991–1992 to 48% in 1998–1999; \( P < .001 \)), with 22% of the antimicrobials used to treat viral illnesses (e.g., common colds or unspecified upper respiratory tract infections) [1]. In the most recent survey period, macrolides, fluoroquinolones, and third-generation cephalosporins comprised 13%, 16%, and 12%, respectively, of antimicrobial prescriptions for adults.

The widespread use of fluoroquinolones is often inappropriate, and this usage pattern can affect microbial susceptibility patterns. In a study of 100 consecutive patients who were discharged from the emergency department of an academic medical center and who received fluoroquinolone therapy, 81 (81%) received the agent for an inappropriate indication (e.g., there was no infection, or fluoroquinolone was not the first-line agent), and only 1 (1%) of the patients for whom therapy was appropriate both received the correct dose and followed the correct duration of treatment [2]. Inappropriate use of fluoroquinolones can be associated with significant “collateral damage.” In a study of 35,790 unique, aerobic, gram-negative isolates recovered from patients in intensive care units (ICUs) across the United States, resistance to quinolones increased from 14% in 1994 to 24% in 2000 for all isolates and, most notably, from 16% to 32% for
**Pseudomonas aeruginosa** isolates [3]. This decrease in activity coincided with a 2.5-fold increase in the national use of fluoroquinolones (r = 0.976 and P < .001, for *P. aeruginosa*; r = 0.891 and P = .007, for gram-negative bacilli). These findings are especially troubling, because it was not long ago that ciprofloxacin was considered to be the “drug of choice” for treating pseudomonal infections. Furthermore, resistance to fluoroquinolones was associated with cross-resistance to several other broad-spectrum agents (e.g., aminoglycosides, third-generation cephalosporins, and carbapenems).

**IMPACT OF RESISTANCE ON OUTCOMES**

Nosocomial infections increase mortality rates among critically ill patients, with nosocomial pneumonia being no exception. In a case-control study, Fagon et al. [4] showed that half of deaths occurring among patients undergoing ventilation were attributable to nosocomial pneumonia. Identity of the causative pathogens, use of inappropriate antimicrobial therapy, and severity of illness were identified as risk factors for the attributable mortality [4, 5].

**Identity of the causative pathogens.** Although pathogens of primarily endogenous origin (i.e., those colonizing patients at admission to the ICU) generally do not affect mortality for patients treated with appropriate antimicrobial therapy, gram-negative bacilli acquired during an ICU stay and those acquired from an exogenous source (e.g., from a ventilator circuit) cause significant excess mortality [6, 7]. In a prospective, cohort study of patients with late-onset ventilator-associated pneumonia (VAP) (i.e., VAP occurring ≥96 h after intubation), Kollef et al. [8] found that infection due to high-risk pathogens (i.e., nonfermenting gram-negative bacilli) was the most important predictor of in-hospital mortality (adjusted OR, 5.4; P = .009). In a case-control study of nosocomial pneumonia in patients undergoing ventilation, the attributable mortality rate was 43%, and the relative risk (RR) of death was 2.5 when either *P. aeruginosa* or *Acinetobacter* species was the infecting pathogen [4]. Infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) has a similar detrimental effect on mortality. In a study by Rello et al. [9], the mortality rate was ≥20-fold higher among patients with VAP caused by MRSA than among patients with VAP caused by methicillin-susceptible strains of *S. aureus*. However, these data do not tell us whether it is the virulence of the pathogen or the propensity to treat these organisms incorrectly with initial empirical therapy that is responsible for the observed increased mortality rate.

**Inadequate antimicrobial therapy.** Accumulating evidence shows that the selection of antimicrobial therapy and the timing of its administration are important determinants of death for critically ill patients with serious infections (figure 1) [10–15]. In a prospective, matched cohort study conducted by Heyland et al. [16], the attributable risk of death was higher for medical service patients (RR for increase, 65%) than for surgical service patients (RR for increase, −27%; P = .04), perhaps as a result of differences in underlying chronic diseases, and it was higher for patients who were administered inappropriate antimicrobial therapy (RR for increase, 60%) than for patients who were administered appropriate therapy (RR for increase, 20%; P > .05). By use of serial quantitative bacteriological tests during therapy for VAP, Baughman and Kerr [17] documented a significantly higher mortality rate among patients without clearance of bacteria (i.e., >100 cfu/mL of bronchoalveolar lavage [BAL] fluid) (mortality rate, 79%) than among patients with clearance of bacteria (mortality rate, 36%) at days 2–5 of therapy, thus emphasizing the need to select therapy capable of reducing the bacterial burden in the lower respiratory tract within the first few days of therapy for VAP. Luna et al. [12] determined that, if appropriate antimicrobial therapy is delayed until after microbiological results for a BAL sample are known, the mortality rate for patients with VAP is higher than it is if the correct antimicrobial agents are initiated at the time of clinical diagnosis (figure 2). These findings underscore the importance of providing the right antimicrobial agent in a timely fashion to patients with VAP. The primary reason that patients receive inappropriate antimicrobial therapy is the presence of antimicrobial-resistant bacteria (discussed below) [14]. Therefore, the selection of empirical treatment for VAP should be broad enough to cover the most likely pathogens, including antimicrobial-resistant strains, if they are suspected.

**MODIFYING EMPIRICAL THERAPY**

Given the importance of appropriate antimicrobial therapy to prognosis, investigators have conducted studies to evaluate, on the basis on microbiologic data, the impact that modification of empirical antimicrobial therapy has on outcome. Most stud-
ies have shown that delaying the start of therapy or modifying an inappropriate antimicrobial regimen does not improve outcome [18], most likely because the change comes too late to redirect the course of illness.

Sanchez-Nieto et al. [19] found that changes in antimicrobial therapy were more common for patients with VAP diagnosed by fiberoptic bronchoscopy methods than for patients whose VAP was diagnosed by quantitative assessments of endotracheal aspirates but that there were no differences in mortality between the 2 groups of patients. In a prospective, single-center cohort study of patients with VAP for whom the antimicrobial agent used was determined by mini-BAL culture results, 51 had antimicrobial therapy delayed or changed, 28 had antimicrobial therapy discontinued, and 51 had no change in their therapy [13]. The in-hospital mortality rate was significantly greater for the subgroup of patients who began therapy late or whose antimicrobial regimen was changed, compared with the other 2 subgroups (mortality rates of 61%, 14%, and 33%, respectively). These results are consistent with those from the study by Luna et al. [12], in which mortality rates were no better among patients with VAP whose antimicrobials were adjusted on the basis of BAL culture results than among patients who continued to receive inadequate therapy. In that study, most of the changes in therapy were necessary, because the initial antimicrobial choice was inappropriate. Although such changes from incorrect to correct therapy are necessary, they may be harmful and should be distinguished from changes that are meant to focus and streamline (de-escalate) therapy, which are discussed below.

**DE-ESCALATION OF INITIAL BROAD-SPECTRUM THERAPY**

A de-escalation strategy—that is, initial broad-spectrum antimicrobial therapy followed by a narrowing of the spectrum to specific therapy, on the basis of culture results—is preferred to a strategy of switching from narrow-spectrum (but incorrect) to broad-spectrum (but correct) agents. Initial, broad-spectrum antimicrobial coverage increases the likelihood that in vitro activity against the infecting pathogen will be present and provides maximum benefit for critically ill patients with severe infection. This should be followed by switching to narrower-spectrum therapy that is directed by culture results, to minimize the emergence of resistance [20–23]. According to a study by Trouillet et al. [20], broad-spectrum therapy was required for efficacy against the potentially multiresistant pathogens causing late-onset VAP. Empirical therapy with the combination of imipenem, amikacin, and vancomycin provided the broadest in vitro activity (susceptibility, 88%) against the organisms recovered in their ICU (e.g., MRSA, *P. aeruginosa*, and *Acinetobacter* species). An ICU-specific treatment protocol for VAP, like that suggested by the data of Trouillet et al. [20], could be developed by medical centers on the basis of knowledge of the most common organisms isolated and their sensitivity patterns in the ICU. The value of this approach was studied by Ibrahim et al. [24] at Washington University School of Medicine (St. Louis). Their clinical guidelines suggested that all patients with VAP be treated empirically for *P. aeruginosa* and MRSA with vancomycin, imipenem, and ciprofloxacin (on the basis of their local susceptibility data), that therapy be modified on the basis of culture results after 24–48 h, and that administration of antimicrobial agents be stopped after 7 days, unless the patient’s clinical status requires longer treatment. When the findings for 52 consecutive patients treated after implementation of these guidelines were compared with the findings for 50 patients treated before implementation of these guidelines, the investigators observed that (1) a higher proportion of patients were treated with appropriate therapy (94% vs. 48%; *P* < .001), (2) the duration of antimicrobial treatment was shorter (14.8 vs. 8.6 days; *P* < .001), and (3) the incidence of a second episode of VAP was lower (8% vs. 24%; *P* = .03), but that there were no differences in mortality.

**COMBINATION THERAPY VERSUS MONOTHERAPY**

There is a lack of compelling data to support the initial use of combination therapy for broad-spectrum coverage. In a meta-analysis of data from 64 randomized trials of 7586 nonneutropenic patients with sepsis, combination therapy that included an aminoglycoside and a *β*-lactam offered no benefit over *β*-lactam monotherapy, on the basis of all-cause mortality.
(RR, 0.90), and the rate of nephrotoxicity was higher in patients treated with the aminoglycoside (RR, 0.36) [25]. Interestingly, the comparison favored monotherapy for clinical failure (RR, 0.87) and bacteriologic failure (RR, 0.86), as well as bacterial superinfections (RR, 0.79). Despite these findings, consensus opinion suggests that a 2-drug combination containing an aminoglycoside be used initially when pseudomonal infection is suspected [26]. For nonpseudomonal infections, ciprofloxacin, imipenem, [27] meropenem, cefpirome, piperacillin/tazobactam, and, possibly, levofloxacin [28] have been shown to give good clinical results when used as monotherapy and, therefore, are suggested as components of initial combination therapy that can be de-escalated, once the presence of a multidrug-resistant pathogen is excluded.

When making choices for empirical therapy for VAP, one must be mindful of pseudomonal resistance, which is highly dependent on recent antimicrobial use. Using multivariate regression analysis, Trouillet et al. [29] identified, among other factors, previous fluoroquinolone use (OR, 4.6) as an independent risk factor, among patients in an ICU, for the development of VAP caused by piperacillin-resistant P. aeruginosa. More recently, Nseir et al. [30] found that, among patients treated with a fluoroquinolone, compared with control subjects who were not treated with a fluoroquinolone, the percentage of patients in the ICU who became infected with multidrug-resistant bacteria was ~2-fold higher (P = .028). Specifically, MRSA (26% vs. 12%; P = .028) and extended-spectrum β-lactamase–producing gram-negative bacilli (11% vs. 1%; P = .017) were isolated more frequently from patients who received fluoroquinolone therapy. Because critically ill patients will often have multiple infections, these data suggest that, perhaps, fluoroquinolones should be avoided for the first ICU-acquired infection, to preserve their usefulness for infections that occur later during the hospital stay, because their use for an initial infection could make the subsequent use of both quinolones and β-lactams less effective [31].

In a prospective study of VAP caused by multidrug-resistant Acinetobacter baumannii, Garnacho-Montero et al. [32] compared the efficacy and toxicity of intravenous colistin (21 patients infected with strains susceptible only to colistin) with those of imipenem (14 patients infected with imipenem-susceptible strains) alone or combined (6 patients) with another antimicrobial agent (i.e., sulbactam, 3 patients; amikacin, 2 patients; and tobramycin, 1 patient). The treatment groups were similar on the basis of clinical cure rate (57% each), in-hospital mortality rate (62% and 64%, respectively), VAP-related mortality rate (38% and 36%, respectively), and rates of toxicity (i.e., renal failure or polyneuropathy). Some researchers have advocated the use of a carbapenem even to treat VAP caused by carbapenem-resistant A. baumannii, although data to support this strategy are lacking, and colistin appears to be an effective alternative against this pathogen.

Infections due to gram-positive pathogens, including methicillin-resistant S. aureus and strains of Streptococcus pneumoniae with reduced susceptibility to penicillin, are increasing in frequency [33]. Rates of empirical and therapeutic use of vancomycin have increased in response to these trends, leading to concerns about potential pressure toward the development of resistance to vancomycin. Fortunately, there are alternatives for treating infections caused by these resistant gram-positive cocci, including streptogramins (e.g., quinupristin/dalfopristin), linezolid, tigecycline, daptomycin, and agents in development (e.g., dalbavancin and telavancin) for nosocomial strains. Daptomycin should not be used to treat pneumonia, because the drug is inactive in the presence of surfactant.

Kollef et al. [34] retrospectively analyzed data from 2 randomized, double-blind studies in which linezolid was compared with vancomycin, each in combination with aztreonam, for the treatment of patients with suspected gram-positive VAP. Multivariate regression analysis showed that treatment with linezolid was an independent predictor of clinical cure and survival for patients with gram-positive VAP (OR, 2.4 and 2.6, respectively) and for patients with VAP caused by MRSA (OR, 20.0 and 4.6, respectively).

**CONTROLLING RESISTANCE BY PROPER DURATION OF THERAPY**

For patients receiving appropriate antimicrobial therapy, clinical resolution of pneumonia usually begins during the first several days of treatment. Dennesen et al. [35] evaluated various clinical parameters in 27 patients with VAP who received appropriate therapy. Improvements over time were observed for leukocyte count, temperature, and PaO2/FIO2, with the change most evident during the first 6 days of therapy (figure 3) [35].

![Figure 3](image)

**Figure 3.** Clinical signs of infection at baseline and on day 6 of therapy for patients with ventilator-associated pneumonia [35].
Among patients with abnormalities at baseline, the mean (median) duration of resolution was 5 (3) days for temperature, 6 (2) days for \( \text{Pao}_2/\text{Fio}_2 \) ratio, and 8 (6) days for leukocyte count.

Of note, \textit{Haemophilus influenzae}, \textit{S. pneumoniae}, and \textit{S. aureus} were eradicated from all endotracheal aspirates. In contrast, despite prolonged therapy, persistent colonization with \textit{P. aeruginosa} was observed in all patients, and several patients acquired tracheal colonization (primarily with \textit{P. aeruginosa}) during the second week of antimicrobial therapy. In a prospective, multicenter study, Luna et al. [36] evaluated the clinical pulmonary infection score (CPIS; i.e., temperature, leukocytosis, tracheal secretions, \( \text{Pao}_2/\text{Fio}_2 \) ratio, and findings on chest radiographs) as an early predictor of outcome during therapy for 63 patients with VAP. The CPIS worsened from 3 days before to the day of the onset of VAP (\( P < .001 \)) and then improved (i.e., decreased) steadily over the next 7 days, significantly so by as early as the third day of therapy for survivors, but not for nonsurvivors (figure 4) [36]. The mortality rate was significantly lower among patients with a CPIS of <6 at either day 3 or 5 of treatment (mortality rate, 34.4%) than among patients with a CPIS of \( \geqslant 6 \) (mortality rate, 67.7%; \( P = .018 \)). These data challenge the idea that antimicrobial therapy for VAP is needed for 14–21 days, because most patients get better very quickly. By establishing a CPIS threshold value below which treatment should be continued for 2–3 days and then discontinued, CPIS may be useful in defining the duration of therapy.

The effect of shortening the duration of antimicrobial therapy was evaluated by Chastre et al. [37] in a multicenter, double-blind study in which 401 patients with microbiologically confirmed VAP were randomized to receive therapy for 8 or 15 days. There were no differences between treatment groups on the basis of various end points, including length of stay in the ICU, incidence of recurrent infections, number of mechanical ventilation–free days, number of organ failure–free days, and mortality rate at day 60. Patients infected with nonfermenting gram-negative bacilli (e.g., \textit{P. aeruginosa}) and treated for 8 days had a higher rate of recurrence of infection than did patients infected with the same pathogens who were treated for 15 days (41% vs. 25%; \( P = .06 \)). Among patients with recurrent infection, multidrug-resistant pathogens emerged less frequently in patients treated for a shorter period (42% vs. 62%; \( P = .04 \)). More recently, Micek et al. [38] randomized patients who were being treated for clinically suspected VAP according to protocol (i.e., with cefepime, ciprofloxacin or gentamicin, plus vancomycin or linezolid, which was the appropriate therapy for 94% of patients) to receive treatment for a duration determined either by policy or by the treating physicians. According to the policy, antimicrobial therapy should be discontinued if there was a noninfectious etiology or if infection resolved (i.e., temperature was <38.3°C, WBC count was <10,000 cells/µL, findings on chest radiographs were stable or improved, no purulent sputum was present, and the \( \text{Pao}_2/\text{Fio}_2 \) ratio was >250). The duration of therapy was shorter for the group of patients whose therapy was discontinued on the basis of policy, compared with patients whose therapy was not defined by the treating physician (6 vs. 8 days; \( P = .001 \)), with no differences between groups with regard to occurrence of second VAP episodes, length of stay in the ICU, or in-hospital mortality rate.

For patients with VAP who are at a high risk of infection due to multidrug-resistant pathogens, initial therapy with aerosolized antimicrobial agents, combined with systemically administered agents, may result in good clinical outcomes and permit shortening the duration of treatment [39]. This finding is in contrast to those of previous experiences with aerosol administration of antimicrobials for the prevention of pneumonia in seriously ill patients [40]. Given the poor distribution of aminoglycosides from serum into respiratory secretions (40%) and the high risk of toxicity, targeted adjunctive therapy with aerosolized aminoglycosides, used with parenteral administration of either the same or another class of antimicrobial agents, may facilitate successful treatment of multidrug-resistant strains. Aerosolized delivery of aminoglycosides provides local concentrations that exceed by several fold those achieved with parenteral administration without systemic toxicity [41].

**PATHOGENS CAUSING INFECTION AND IMPLICATIONS FOR TREATMENT**

For patients who experience onset of infection within the first 4 days of hospitalization and who have none of the risk factors for health care–related pneumonia or multidrug-resistant pathogens listed in table 1 [26], \textit{S. pneumoniae}, methicillin-susceptible \textit{S. aureus}, \textit{H. influenzae}, and antimicrobial-susceptible enteric gram-negative bacilli (e.g., \textit{Klebsiella pneumoniae} and \textit{Enterobacter} species) are the most common causative pathogens
In certain regions of the country and after documented cases of influenza or influenza-like illness, community-acquired MRSA should also be considered (as discussed elsewhere in this supplement by L. Clifford McDonald [33]). For patients who develop severe infection later during their hospital stay or for patients with the risk factors listed in table 1, additional antimicrobial-resistant bacteria (e.g., *P. aeruginosa*, *Acinetobacter* species, and MRSA) may also be responsible for infection [42, 43]. For instance, in the study by Luna et al. [12], *S. aureus* (63% of strains were methicillin resistant), *Acinetobacter* species, *K. pneumoniae*, and/or *P. aeruginosa* were the pathogens most commonly isolated from BAL fluid, with *S. aureus* and/or *Acinetobacter* species involved in the majority (74%) of episodes. These highly antimicrobial-resistant organisms have been most commonly associated with inadequate antimicrobial therapy in patients with culture-positive VAP [43].

Prior antimicrobial use increases the risk of infection caused by multidrug-resistant pathogens in critically ill patients. This point was demonstrated by Trouillet et al. [20], who prospectively observed 135 consecutive episodes of VAP. Using multivariate analysis, they found that duration of mechanical ventilation of $\geq 7$ days before occurrence of the VAP episode (OR, 6.0), use of antimicrobials within the past 15 days (OR, 13.5), and prior use of broad-spectrum drugs (third-generation cephalosporins, fluoroquinolones, and/or imipenem; OR, 4.1) were significant risk factors for infection with drug-resistant bacteria. In patients undergoing mechanical ventilation for $\geq 7$ days and with prior antimicrobial use, the frequency of multidrug resistance was 59%, versus 0% in patients with early-onset VAP who did not have the risk factors. The same trend was observed by Rello et al. [42], who also showed that the specific bacterial causes of VAP vary markedly by treatment site. Thus, the probability of multidrug-resistant pathogens causing VAP is greatest in patients with prolonged ICU and hospital stays, patients who were treated previously with an antimicrobial agent, and patients with prolonged duration of mechanical ventilation [8, 26]. Clinicians should select empirical antimicrobial agents for critically ill patients on the basis of the patients’ probability of being infected with a multidrug-resistant pathogen (table 1) and on the basis of up-to-date data on the susceptibility patterns of multidrug-resistant isolates in their own ICU.

**MULTIDRUG-RESISTANT BACTERIA PREDISPOSE TO INAPPROPRIATE THERAPY**

Infection caused by an antimicrobial-resistant organism has been associated with delayed initiation of an effective antimicrobial agent (72 h from the time that the specimen was sent for culture, vs. 12 h for infections due to susceptible organisms; $P<.001$) [44] and inappropriate antimicrobial therapy for VAP (figure 5) [45]. In a study conducted by Alvarez-Lerma [10], initial therapy was inappropriate for 50% of patients infected with *Acinetobacter* species, 37% of patients infected with *P.
**Figure 6.** Management strategies for patients with hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), or health care–associated pneumonia (HCAP). LRT, lower respiratory tract. Reprinted with permission from Niederman et al. [26].

*P. aeruginosa,* and 30% of patients infected with *S. aureus,* resulting in a need for modification of therapy and, consequently, increased mortality. Kollef and Ward [13] found that the most common reason for inappropriate antimicrobial therapy and the need for modification was infection caused by ceftazidime-resistant gram-negative bacteria (52% of patients). Other patients needed to have vancomycin added for coverage of MRSA or had an infection due to gram-negative bacteria that were resistant to aminoglycosides, ciprofloxacin, and imipenem [13]. Increasing clinicians’ suspicion of multidrug-resistant pathogens in high-risk, critically ill patients with infection will promote prompt treatment with appropriate antimicrobial agents, which could improve outcomes and decrease the rate of emergence of resistance.

**GUIDELINES FOR TREATMENT OF NOSOCOMIAL PNEUMONIA**

The need for early, appropriate therapy may drive aggressive use of antimicrobials and the potential for overuse, which will lead to more resistance and, then, to more inappropriate therapy. A sensible approach that optimizes patient outcomes while being mindful of responsible antimicrobial stewardship is the subject of great debate.

Earlier this year, the American Thoracic Society and the Infectious Diseases Society of America published new guidelines for the treatment of nosocomial pneumonia, including health care–associated pneumonia and VAP (figure 6) [26]. Health care–associated pneumonia (i.e., pneumonia that develops in patients who were hospitalized during the preceding 90 days, residents of nursing homes or extended-care facilities, recipients of intravenous antimicrobial therapy administered at home, chemotherapy recipients, individuals receiving wound care during the preceding 30 days, and patients receiving long-term dialysis) was added to the spectrum of hospital-associated pneumonia and VAP, on the basis of the risk of and need for empirical therapy directed at multidrug-resistant pathogens. The guidelines emphasize analysis of the modifiable risk factors for infection and tracking of the incidence of multidrug-resistant pathogens, such as *P. aeruginosa,* Acinetobacter species, and MRSA.

According to the new guidelines, diagnosis can be made on the basis of either a clinical approach (supplemented with semiquantitative cultures) or a microbiological approach (relying on quantitative cultures), with the choice based on local expertise. With either approach, a sample from the lower respiratory tract (a tracheal aspirate or other samples, obtained with or without bronchoscopy) should be obtained from all patients. Broad-speci-
trum antimicrobial therapy should be initiated early during the course of illness and at adequate doses; de-escalated, as appropriate, on the basis of culture results and clinical response; and administered for the minimum effective period. In so doing, excessive antimicrobial use can be avoided while positive patient outcomes are maximized. Empirical therapy with highly effective agents that are rapidly bactericidal, administered in a timely manner, could theoretically minimize the emergence of resistance [46]. Furthermore, administration of drugs on the basis of pharmacokinetic principles may improve our ability to treat multidrug-resistant pathogens effectively and combat the emergence of resistance. For instance, infusing the same dose of meropenem over the course of 3 h, instead of 30 min, was shown to increase the likelihood of attaining the maximum cell-kill target [47, 48]. Of note, the American Thoracic Society/Infectious Diseases Society of America evidence-based guidelines for nosocomial pneumonia are based on studies of VAP, because well-conducted studies involving patients who are not undergoing mechanical ventilation are lacking. Nonetheless, patients who are not intubated or undergoing mechanical ventilation should be treated in the same manner as those with VAP.

The guidelines offer specific recommendations for empirical treatment, although, ultimately, the choice of agent should be based on ICU-specific trends in pathogens and their susceptibility patterns. For patients who experience onset of infection within the first 4 days of hospitalization and who have no risk factors for infection with multidrug-resistant pathogens, limited-spectrum antimicrobial therapy is appropriate (i.e., ceftriaxone, a fluoroquinolone, ampicillin/sulbactam, or ertapenem) for coverage against penicillin-susceptible S. pneumoniae, H. influenzae, and antimicrobial-susceptible enteric gram-negative bacilli (e.g., K. pneumoniae and Enterobacter species) [26]. For patients with late-onset infection (i.e., infection that occurs ≥5 days after hospitalization) or with risk factors for infection with multidrug-resistant pathogens (table 1), broad-spectrum (combination) antimicrobial therapy should be initiated promptly, with a commitment to de-escalating therapy on the basis of serial clinical and microbiologic data. The recommended combinations include an antipseudomonal cephalosporin, an antipseudomonal carbapenem (which is reliable if an extended-spectrum β-lactamase–positive strain is suspected), or a β-lactam/β-lactamase inhibitor plus either an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside (plus a macrolide if Legionella pneumophila is suspected) plus either vancomycin or linezolid (if MRSA is suspected). If an aminoglycoside is one of the agents used, discontinuation should be considered after 5 days of therapy, because incremental clinical benefit thereafter is minimal and because the potential for toxicity is significant.

VAP is a well-studied model from which principles that are generalizable to other severe infections can be drawn. Keeping in mind the same considerations as those discussed in the present article, the Infectious Diseases Society of America has developed and issued treatment guidelines for the treatment of diabetic foot infections [49] and intra-abdominal infections [50].

CONCLUSIONS

Appropriate use of antimicrobial agents—that is, striking the balance between maximizing clinical outcomes and minimizing selection of resistant organisms—will require a multifaceted approach. Among the initiatives will be antimicrobial agent control programs, surveillance of local resistance patterns, prompt use of adequate empirical therapy (proper antimicrobial agents and doses), use of combination therapy when needed, de-escalation of therapy whenever possible, shorter duration of therapy, and, perhaps, cycling of antimicrobials [51, 52]. Any one initiative alone probably will have a limited impact. For example, Rahal et al. [53] evaluated the incidence of infection or colonization by ceftazidime-resistant K. pneumoniae in the year before and after restriction of cephalosporins (i.e., use of the drugs was prohibited for all medical and surgical service patients, and other uses required preapproval by an infectious diseases specialist) at one university-affiliated community hospital. Restriction led to an 80% decrease in cephalosporin use and a 140% increase in imipenem use, which was associated with a 44% hospital-wide decrease in the prevalence of third-generation cephalosporin-resistant K. pneumoniae (P<.01) and a troubling 68% hospital-wide increase in the prevalence of imipenem-resistant P. aeruginosa (P<.01). Burke [54] described this “transfer” of resistance from one antimicrobial class and pathogen to another with cephalosporin class restriction as “squeezing the balloon”. Squeezing the resistance balloon at multiple sites is needed to control resistance (i.e., restriction of antimicrobial agents to control polyclonal resistance and infection-control procedures should be directed at pathogens exhibiting clonal resistance) [55].

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