Drugs 2003; 63 (20): 2157-2168
0012-6667/03/0020-2157/$33.00/0

Appropriate Empirical Antibacterial Therapy for Nosocomial Infections

Getting it Right the First Time

Marin H. Kollef

Pulmonary and Critical Care Division, Washington University School of Medicine, St Louis, Missouri, USA

Abstract

The increasing presence of drug-resistant bacterial infections among hospitalised patients has resulted in greater numbers of patients receiving inappropriate antimicrobial treatment. This has led to the development of a novel paradigm guiding the administration of empirical antimicrobial therapy for patients with serious infections in the hospital setting. Antibacterial de-escalation is an approach to antibacterial utilisation that attempts to balance the need to provide appropriate, initial antibacterial treatment while limiting the emergence of antibacterial resistance. The goal of de-escalation is to prescribe an initial antibacterial regimen that will cover the most likely bacterial pathogens associated with infection while minimising the emergence of antibacterial resistance. Antibacterial resistance is minimised by narrowing the antibacterial regimen once the pathogens and their susceptibility profiles are determined, and by employing the shortest course of therapy clinically acceptable.

There is a general consensus that antimicrobial resistance in the hospital setting has emerged as an important variable that influences patient outcomes and overall resource utilisation.[1-3] Hospitals worldwide are faced with increasingly rapid emergence and spread of resistant bacteria. Both antibacterial-resistant Gram-negative bacilli and Gram-positive bacteria are reported as important causes of hospital-acquired infections.[4,5] In many cases, few antibacterial agents remain for effective treatment, particularly with methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* and Gram-negative bacteria producing extended-spectrum β-lactamase (ESBL) with resistance to multiple other antibacterials.[6-8]

The increasing presence of resistant bacterial infections among hospitalised patients is probably related to the numerous pressures promoting resistance as well as the administration of inappropriate antibacterial therapy. These pressures include: (i) the frequent use of broad-spectrum antibacterials; (ii) prolonged use of antibacterials; (iii) crowding of patients with high levels of disease acuity within relatively small specialised areas of the hospital; (iv) reductions in nursing and ancillary support staff as a result of economic pressures, which increase the

likelihood of person-to-person transmission of resistant bacteria; and (v) the presence of more chronically and acutely ill patients who require prolonged hospitalisations and often harbour resistant bacteria.[9-11] This review focuses on antibacterial resistance, the importance of administering initial appropriate antibacterial treatment for serious infections and antibacterial de-escalation as it applies to hospital-acquired infections, especially hospital-acquired pneumonia (HAP). Despite the limited class IA evidence (i.e. data from prospective, blinded, randomised trials) in support of these strategies, clinical practices are evolving based on the clinical experiences described in this review.

1. Importance of Appropriate Initial Antimicrobial Therapy

One of the consequences of an increase in antimicrobial resistance has been an increased recognition of inappropriate antimicrobial treatment of infections.[12] Inappropriate antimicrobial treatment of serious infections in the hospital setting has been demonstrated to be an important determinant of hospital mortality.[13-15] Inappropriate antimicrobial treatment represents the use of antimicrobials with poor or no *in vitro* activity against the identified microorganisms causing infection at the tissue site of infection. Examples of inappropriate treatment include the absence of antimicrobial agents directed at a specific class of microorganisms (e.g. absence of therapy for fungaemia due to *Candida* species) and the administration of antimicrobial agents to which the microorganism responsible for the infection are resistant (e.g. empirical treatment with nafcillin for pneumonia subsequently attributed to MRSA). Changing antimicrobial therapy based on the subsequent available culture results and antibacterial susceptibilities may not reduce the excess risk of hospital mortality associated with inappropriate initial antibacterial treatment.[16,17] Therefore, the selection of initial appropriate therapy (i.e. getting antibacterial treatment right the first time) is an important aspect of care for hospitalised patients with serious infections.

Most inappropriate antimicrobial treatment of hospital-acquired infections appears to be related to bacteria resistant to the prescribed agents.[12-18] Although inappropriate antibacterial treatment may explain, in part, the greater mortality rates associated with resistant bacterial infections, other factors may also contribute to this excess mortality. Resistant Gram-positive bacteria such as MRSA express a number of virulence factors, which potentially contribute to their higher rates of associated mortality.[19,20] However, not all investigators have demonstrated greater mortality rates with infections due to MRSA compared with methicillin-susceptible *S. aureus*.[21] Similarly, some resistant Gram-negative bacteria (e.g. *Pseudomonas aeruginosa*) are associated with increased virulence factors compared with susceptible pathogens.[22,23] This may explain the excess attributable mortality observed with infections due to these pathogens as well.

Hospital-acquired bloodstream infections are among the most serious infections acquired by intensive care unit (ICU) patients. Antibacterial resistance appears to have contributed to the increasing administration of inappropriate antibacterial therapy for hospital-acquired bloodstream infections, which is associated with greater hospital mortality rates.[13,14,24,25] The problem of antibacterial-resistant bacteraemia also appears to be increasing both in the hospital setting as well as in the community.[26] Given the current trend of greater severity of illness for critically ill patients, it can be expected that infections due to resistant bacterial strains will be associated with greater morbidity and mortality, particularly when inappropriate empirical antibacterial therapy is administered.[12] Along with greater patient mortality rates, infections due to resistant bacteria and inappropriate antibacterial treatment are associated with prolonged hospitalisation

Table I. Potential strategies to limit the emergence of antibacterial resistance in the hospital setting

Optimise antibacterial effectiveness
Prescribe initial appropriate empirical treatment based on local pathogen prevalence and antibacterial susceptibility
Use combination antibacterial treatment to cover the most common bacterial pathogens
Provide education and professional detailing to clinicians on appropriate antibacterial therapy
Use locally developed antibacterial management guidelines
Consult with local infectious disease specialists
Use antibacterial cycling and scheduled antibacterial changes according to changing patterns of pathogens and antibacterial susceptibility
Consider the use of area-specific empirical antibacterial regimens in larger hospitals because of area-specific variability in pathogens and their susceptibility patterns
Limit unnecessary antibacterial utilisation
De-escalation approach to therapy
use narrow-spectrum or older antibacterials based on patient risk profile and culture results
use the shortest course of antibacterial therapy that is clinically indicated
Avoid prolonged use of prophylactic antibacterials
Apply selective formulary control or restriction of specific 'problem' antibacterial agents or drug classes
Develop/apply local guidelines or protocols detailing optimal indications for and durations of antibacterial treatment
Use quantitative cultures, when appropriate, to establish diagnostic thresholds for treating specific infections

and increased healthcare costs relative to infections due to susceptible bacteria.[15,27,28] The overall US national costs of antibacterial resistance have been estimated to be between $US100 million and $US30 billion (2000 values) annually for the control and treatment of infections caused by resistant bacteria.[29]

In addition to selecting the most appropriate antimicrobial agents for the treatment of serious infections, clinicians must ensure that antibacterial administration follows certain minimal requirements. These minimal requirements include proper dose, interval administration, optimal duration of treatment, monitoring of drug concentrations when appropriate and avoidance of unwanted drug interactions.[30] Lack of adherence to these minimal requirements can result in unforeseen administration of suboptimal or excessive antibacterial tissue concentrations, which increases the likelihood for antibacterial resistance, patient toxicity and lack of effectiveness despite selecting an appropriate antibacterial regimen.[31]

2. The De-Escalation Approach to Antibacterial Utilisation

Ideally, clinicians should prescribe antibacterial therapy with the goals of providing appropriate initial therapy to hospitalised patients with serious infections and minimising the emergence of bacterial resistance. Various strategies for the prevention of antibacterial resistance have been proposed in terms of improving overall antibacterial utilisation.[32,33] Table I highlights several of these strategies aimed at either limiting the unnecessary use of antibacterials or optimising their effectiveness when prescribed to hospitalised patients. Antibacterial de-escalation is one approach to antibacterial utilisation that attempts to balance the need to provide appropriate initial treatment while limiting the emergence of antibacterial resistance (figure 1).

An effective approach to antibacterial de-escalation necessitates that clinicians be aware of the bacteria that are most likely to be associated with infection and inappropriate antibacterial treatment in their practice setting. This requires that hospitals have updated and accurate antibiograms reflecting the bacterial pathogens and their antibacterial sus-

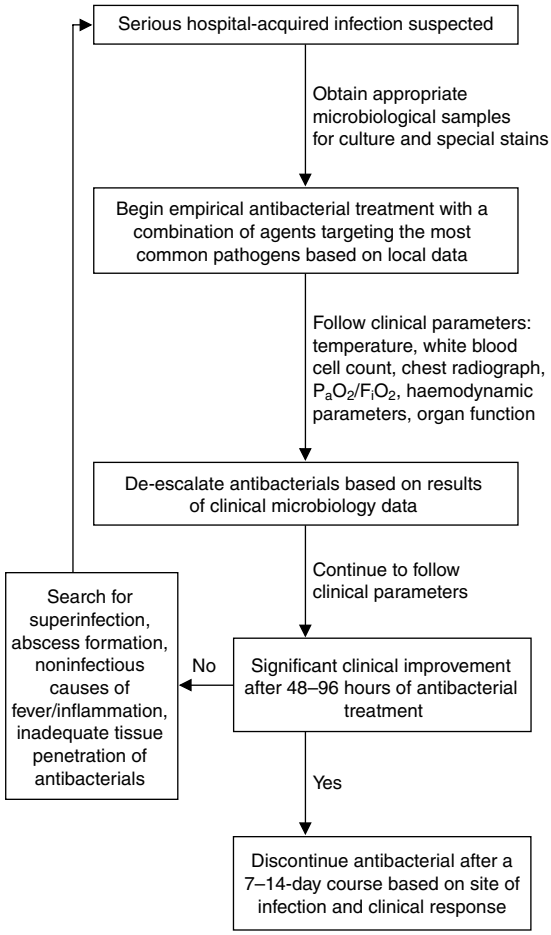

Fig. 1. A flow diagram illustrating the de-escalation approach to antibacterial treatment for hospital-acquired infections. $\mathbf{F_iO_2}$ = inspired oxygen fraction; $\mathbf{P_aO_2}$ = partial pressure (or tension) of arterial oxygen.

ceptibility encountered at the local level. Variability in the bacteria associated with hospital-acquired infections among hospitals, as well as within the wards of large hospitals, has been demonstrated to occur.[34,35] Additionally, changing temporal patterns of nosocomial pathogens and antibacterial susceptibility have been described.[36] This suggests that hospitals may need to develop systems for updating local antibiograms on a regular basis because of the potential existence of intra-hospital and temporal variations. Using such data can improve the efficacy of antibacterial therapy by increasing the likelihood that appropriate initial antibacterial treatment will be prescribed to infected patients.[36,37]

In order to de-escalate or narrow the initial empirical antibacterial regimen, clinicians must be able to obtain culture specimens before starting antibacterial therapy. However, it is understood that prolonged delays in the administration of appropriate antibacterial treatment should not occur in seriously ill patients while waiting for specific cultures to be obtained (e.g. bronchoalveolar lavage, cerebral spinal fluid). The most common pathogens associated with the administration of inappropriate antibacterial treatment for hospital-acquired infections include potentially resistant Gram-negative bacteria (*P. aeruginosa*, *Acinetobacter* species, *Klebsiella pneumoniae* and *Enterobacter* species) and *S. aureus*, especially the strains with methicillin resistance.[12-18] Therefore, clinicians should consider initial empirical therapy for these pathogens, especially in patients at high risk for antibacterial-resistant infections.

Clinicians should also be aware that healthcare-acquired infections are similar to hospital-acquired infections in terms of the pathogens responsible for infection.[38-41] Healthcare-acquired infections are defined by a positive culture obtained within 48 hours of hospital admission and one of the following criteria: (i) received intravenous therapy at home, received wound care or specialised nursing care through a healthcare agency, family or friends or had self-administered intravenous medical therapy in the 30 days before the infection; (ii) attended a hospital or haemodialysis clinic or received intravenous chemotherapy in the 30 days before the infection; (iii) was hospitalised in an acute care hospital for ≥2 days in the 90 days before the infection; and (iv) resided in a nursing home or long-term care facility.[38] Physicians should be aware of the factors that identify patients as having healthcare-acquired

infections in order to avoid the prescription of inappropriate antibacterial treatment.

3. Examples of the De-Escalation Approach

Trouillet and co-workers[9] identified risk factors for ventilator-associated pneumonia (VAP) caused by potentially drug-resistant bacteria such as MRSA, *P. aeruginosa*, *Acinetobacter baumannii* and/or *Stenotrophomonas maltophilia* in 135 consecutive episodes of VAP observed in a single ICU over a 25-month period. Seventy-seven (57.0%) episodes of VAP were caused by 'potentially resistant' bacteria and 58 (43.0%) episodes were caused by 'other' non-resistant organisms. According to logistic regression analysis, three variables were predictors for VAP due to potentially drug-resistant bacteria: (i) duration of mechanical ventilation ≥7 days (odds ratio [OR] 6.0; 95% CI 1.6–23.1); (ii) previous antibacterial use (OR 13.5; 95% CI 3.3–55.0); and (iii) previous use of broad-spectrum drugs (third-generation cephalosporin, fluoroquinolone and/or a carbapenem) [OR 4.1; 95% CI 1.2–14.2]. Differences in the potential activities (ranging from 100% to 11%) against microorganisms for 15 different antibacterial regimens were studied to determine their overall level of activity for the pathogens associated with VAP. These investigators observed that the combination of a carbapenem plus amikacin and vancomycin provided the broadest *in vitro* coverage against the spectrum of Gram-negative and Gram-positive bacteria that were found in their ICU. Although clinical outcomes were not assessed, this study suggests that location-specific empirical antibacterial regimens, tailored to the susceptibility patterns of the local flora, are most likely to be effective. Additionally, this study demonstrates that patients at high risk for infection with resistant bacteria can be identified based on risk factors that promote colonisation with such pathogens (e.g. previous antibacterial therapy, and exposure to high-risk environments including hospitals and long-term care facilities).

Ibrahim et al.[37] evaluated 50 consecutive patients in the ICU setting who were receiving antibacterial therapy for VAP. They subsequently examined 52 consecutive patients with VAP whose antibacterial treatment was administered according to a unit-specific antimicrobial guideline. The main goal of the guideline was to provide initial administration of appropriate antimicrobial treatment while avoiding the emergence of antibacterial resistance. This meant providing initial coverage for *P. aeruginosa* and MRSA, the two most common pathogens causing VAP in that specific ICU. This was accomplished by providing initial intravenous combination treatment with vancomycin, a carbapenem and a fluoroquinolone. This combination was selected because it provided *in vitro* coverage for >90% of all the bacterial isolates identified based on a unit-specific antibiogram. The guideline also required that antibacterial treatment be modified after 48 hours based on the available culture results and the clinical course of the patient. In fact, 61.5% of patients had two antibacterials discontinued within 48 hours of beginning therapy based on Gram-stain results from respiratory secretions and culture data.

The second specified goal of the guideline developed by Ibrahim and co-workers[37] was to reduce potentially unnecessary antibacterial administration. This was accomplished by recommending a 7-day course of appropriate antibacterial treatment for patients with VAP. Continued administration of antibacterials beyond day 7 was only encouraged for patients with persistent signs and symptoms consistent with active infection (e.g. fever >38.3°C, circulating leucocyte count >10 000 mm^{-3}, lack of improvement on the chest radiograph, continued purulent sputum). Use of the guideline was associated with a statistically significant increase in the administration of appropriate antibacterial treatment, a decrease in the development of secondary episodes

of antibacterial-resistant VAP and a reduction in the total duration of antibacterial treatment (figure 2).

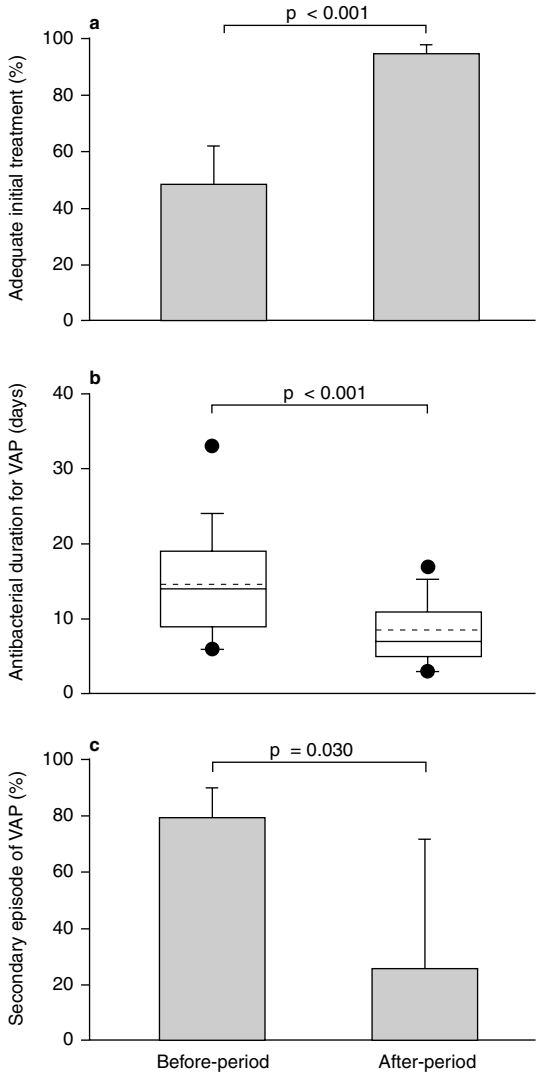

Fig. 2. (**a**) The percentage of control patients (before-period) and intervention patients (after-period) receiving an adequate initial antibacterial regimen. (**b**) The durations of antibacterial treatment for patients with ventilator-associated pneumonia (VAP). Boxes represent the 25th and 75th percentiles with the 50th percentile (solid line) and the mean (dotted line) shown within the boxes. The 10th and 90th percentiles are shown as capped bars, with circles marking the 5th and 95th percentiles. (**c**) The percentage of patients developing a secondary episode of VAP (reprinted from Ibrahim et al.[37] with permission from Lippincott, Williams and Wilkins).

The studies of Trouillet et al.[9] and Ibrahim et al.[37] employed local bacterial susceptibility data in order to develop recommendations for empirical therapy within their respective ICUs. The use of local data should always be taken into consideration when developing empirical regimens for treatment. The American Thoracic Society (ATS) released a consensus statement in 1996 on the diagnosis, assessment, treatment and prevention of HAP that supported the de-escalation approach to antibacterial treatment.[42] This document identifies those microorganisms commonly implicated in HAP and provides antibacterial recommendations based on the infecting pathogens. According to the consensus statement, the management of HAP should be based on the following factors: (i) severity of illness (i.e. mild-to-moderate vs severe as defined in the ATS statement); (ii) presence of risk factors suggesting infection with specific microorganisms (to include the use of local data on pathogens and susceptibility patterns); and (iii) the time of pneumonia onset (i.e. <5 days after hospital admission vs ≥5 days after admission).

The ATS guidelines[42] note that patients with mild-to-moderate disease presenting <5 days after hospitalisation generally are infected with *Haemophilus influenzae*, *Streptococcus pneumoniae*, methicillin-susceptible *S. aureus* or other 'core microorganisms' (i.e. susceptible bacteria). However, the presence of risk factors (e.g. recent abdominal surgery, diabetes mellitus, head trauma, history of high-dose corticosteroids) or local patterns of pathogen prevalence and antibacterial susceptibility can alter the type of predominant infecting microorganism needing coverage. The duration of hospitalisation before the onset of pneumonia is one of the most important determinants for potential infecting pathogens. The risk of infection with MRSA, *P. aeruginosa* and *Acinetobacter* species is increased if nosocomial pneumonia presents after the patient has been hospitalised for >5 days.[43] In

patients with specific risk factors, prolonged hospitalisation or severe disease, combination antibacterial therapy should initially target this broader spectrum of likely infecting bacteria. In addition, combination therapy is required in suspected infections due to *P. aeruginosa* to improve survival rates and reduce the development of antibacterial resistance.[42] Monotherapy may be adequate in some cases of severe nonpseudomonal infection but few studies have evaluated the efficacy of single agents in severe disease.[44-48]

4. Timing of Antibacterial Treatment

A number of investigators have found that delays in the administration of appropriate antibacterial treatment are associated with excess hospital mortality. Alvarez-Lerma[17] showed that among 490 episodes of pneumonia acquired in the ICU setting, 214 episodes (43.7%) required modification of the initial antibacterial regimen as a result of either isolation of a resistant microorganism (62.1%) or lack of clinical response to therapy (36.0%). Attributable mortality from VAP was significantly lower among patients receiving initial, appropriate antibacterial treatment than among patients receiving inappropriate treatment requiring a treatment change (16.2% vs 24.7%; $p = 0.034$).

Iregui and colleagues[49] examined the influence of initially delayed appropriate antibacterial treatment on the outcomes of 107 patients with VAP. All 107 patients eventually received treatment with an antibacterial regimen that was shown *in vitro* to be active against the bacterial pathogens isolated from their respiratory secretions. Thirty-three (30.8%) patients received appropriate antibacterial treatment that was delayed for ≥24 hours after patients initially met diagnostic criteria for VAP. The most common reason for the administration of delayed treatment was a delay in physicians' recognising the presence of VAP and writing the orders for antibacterial treatment ($n = 25$; 75.8%). Patients who receive delayed antibacterial treatment have a statistically greater hospital mortality rate than patients without the delay (69.7% vs 28.4%; $p < 0.001$).

The studies of Alvarez-Lerma[17] and Iregui et al.[49] suggest that delaying the administration of appropriate antibacterial treatment is an important factor contributing to the excess hospital mortality of patients with serious infections. Delays in the administration of appropriate antibacterial treatment have most recently also been associated with greater mortality for patients with severe sepsis.[50,51] These studies demonstrate that initial selection of the 'wrong' antibacterial regimen, because of a lack of efficacy for the identified bacteria(s) associated with infection, will delay appropriate antibacterial delivery to the tissue site of infection and result in worse clinical outcomes.[12]

5. De-Escalation and Antibacterial Resistance

The second goal of antibacterial de-escalation is to avoid the administration of unnecessary antibacterial treatment. First, this requires narrowing the antibacterial coverage after identification of the pathogen to which the infection is attributed and the antibacterial susceptibility profile of the microorganism. Second, the duration of antibacterial treatment should be limited to the shortest effective course of therapy. The following approaches are ways in which unnecessary antibacterial therapy can be avoided in a de-escalation strategy.

5.1 Protocols/Guidelines

Antibacterial practice guidelines or protocols have emerged as a potentially effective means of both avoiding unnecessary antibacterial administration and increasing the therapeutic effectiveness of these agents. The potential benefits of antibacterial use guidelines in the hospital setting have been well demonstrated by the experience at LDS Hospital in Salt Lake City, Utah, USA,[52] which employs a

computerised system guiding antibacterial use. This system has been successfully employed to reduce inappropriate, empirical antibacterial administration compared with individual physician prescribing practices.[52] This automated guideline has also been shown to significantly reduce orders for drugs to which patients were allergic, overall adverse events caused by antibacterials and the total number of anti-infective doses prescribed, as well as the medical costs associated with antibacterial agents.[53]

Nonautomated or partially automated protocols, usually driven by hospital-based quality improvement teams, have demonstrated similar results to those observed with the fully automated antibacterial utilisation systems. In two teaching hospitals, Bailey and co-workers[54] randomised patients to have their physicians contacted by pharmacists with consensus recommendations to discontinue intravenous antibacterials versus no intervention. The intervention significantly reduced the antibacterial doses administered as well as the mean antibacterial costs but was associated with increased labour costs. Similarly, Leibovici and co-workers[55] developed a problem-oriented database decision support system, which significantly reduced the unnecessary use of antibacterials and decreased inadequate antibacterial administration, particularly to patients infected with multiresistant Gram-negative isolates, enterococci and *S. aureus*. With the advent of newly available technologies, including handheld computers and portable communication devices, the ability to extend the influence of treatment protocols to the bedside is becoming increasingly possible.

5.2 Shorter Courses of Antibacterial Therapy

Recently, several groups of investigators have demonstrated that shorter courses of therapy for VAP can be efficacious while reducing the emergence of antibacterial resistance. Singh and co-workers[56] used a scoring system to identify patients with suspected VAP who could be treated with 3 days of antibacterial therapy as opposed to the conventional practice of 10–21 days. Patients receiving the shorter course of antibacterial therapy had clinical outcomes similar to the patients receiving longer therapy, but with fewer subsequent superinfections attributed to antibacterial-resistant pathogens. Similarly, Ibrahim et al.[37] employed a pharmacist-directed protocol in the ICU setting to reduce the empirical administration of antibacterials for suspected VAP from 14.8 ± 8.1 days to 8.1 ± 5.1 days ($p < 0.001$) [figure 2].

Although recommended durations of antibacterial therapy for VAP have generally ranged from 14 to 21 days in the past, these were not based on prospective studies. Dennesen and colleagues[57] evaluated 27 patients with VAP to determine their resolution of signs and symptoms. All patients received appropriate antibacterial therapy, and the highest temperatures, leucocyte counts, oxygen tension in arterial blood to inspired oxygen ratio ($P_aO_2 : F_iO_2$) and semiquantitative cultures of endotracheal aspirates were recorded from the start of therapy until day 14. VAP was caused by Enterobacteriaceae (n = 14), *P. aeruginosa* (n = 7), *S. aureus* (n = 6), *H. influenzae* (n = 3) and *S. pneumoniae* (n = 1). *H. influenzae* and *S. pneumoniae* were eradicated from tracheal aspirates, whereas Enterobacteriaceae, *S. aureus* and *P. aeruginosa* persisted, despite *in vitro* susceptibility to the antibacterials administered. Significant improvements were observed for all clinical parameters, most apparently within the first 6 days after the start of antibacterials. Newly acquired colonisation, especially with *P. aeruginosa* and Enterobacteriaceae, occurred in the second week of therapy. These data support the premise that most patients with VAP receiving appropriate antibacterial therapy respond to treatment within the first 6 days and acquire colonisation with resistant bacteria usually during the second week of therapy, which frequently precedes a recurrent episode of VAP.

The available medical literature suggests that shorter courses of appropriate antibacterial therapy for VAP should be employed because of their equivalent efficacy, compared with longer courses of therapy, and reduced propensity for the emergence of bacterial resistance. A European, multicentre, randomised trial of 8 days versus 15 days of antibacterial treatment for VAP was presented at the ATS meeting; 2003 May 16-21; Seattle (WA), demonstrating equivalent clinical outcomes for both study groups.[58] However, patients randomised to the shorter course of therapy had more antibacterial-free days and the emergence of fewer subsequent infections due to multiresistant Gram-negative bacteria. This represents the first large (n = 401), randomised clinical trial to provide grade IA evidence in support of a shorter duration of therapy for VAP.

5.3 Scheduled Antibacterial Changes/ Antibacterial Cycling/Antibacterial Rotation

Rahal and co-workers[59] introduced a new antibacterial guideline into their hospital that significantly restricted the use of the cephalosporin class. This was done to combat an outbreak of ESBL-producing *Klebsiella* infection. The restriction of cephalosporins was successful, with an 80% reduction in their hospital-wide use accompanied by a 44% reduction in infection and colonisation with the ESBL-producing *Klebsiella* spp. However, the use of imipenem increased by 140% during the intervention year and was associated with a 69% increase in the incidence of imipenem-resistant *P. aeruginosa* throughout the medical centre. Therefore, this represented a change or switch from one predominant antibacterial class to another. Although the number of multipli-resistant pathogens decreased with this formulary restriction, its overall effectiveness can be questioned.

Kollef and co-workers[60] examined the influence of a scheduled antibacterial change on the incidence of nosocomial infections among patients undergoing cardiac surgery. A 6-month 'before-period', during which the traditional practice of prescribing a third-generation cephalosporin (ceftazidime) for the empirical treatment of Gram-negative bacterial infections, was followed by a 6-month 'after-period', during which a fluoroquinolone (ciprofloxacin) was employed. Unexpectedly, the overall incidence of VAP was significantly reduced in the after-period compared with the before-period. This was primarily a result of a significant reduction in the incidence of VAP attributed to resistant Gram-negative bacteria. Similarly, a lower incidence of Gram-negative bacteraemia due to resistant pathogens was observed in the after-period. This experience was followed by a series of scheduled antibacterial changes for the treatment of suspected Gram-negative bacterial infections among patients admitted to the medical and surgical ICUs.[61] The overall prescription of appropriate antibacterial therapy was statistically increased for Gram-negative bacterial infections during this experience.

The concept of antibacterial class cycling or rotation has been advocated as a potential strategy for reducing the emergence of antibacterial resistance.[62] In theory, a class of antibacterials or a specific antibacterial drug is withdrawn from use for a defined time period and reintroduced at a later point in time in an attempt to limit bacterial resistance to the cycled antibacterial agents. Gerding and colleagues[63] evaluated cycling of aminoglycosides over 10 years at the Minneapolis Veterans Affairs Medical Center, Minneapolis, Minnesota, USA, cycling amikacin and gentamicin. Resistance to gentamicin had emerged as a clinical problem limiting the use of that specific aminoglycoside at this hospital. Using cycle times of 12–51 months, these investigators found significantly reduced resistance to gentamicin when amikacin was used, but a return of resistance with the rapid reintroduction of gentamicin, followed by more gradual reintroduction of gentamicin a second time without increased levels

of resistance recurring. This experience suggested that the cycling of antibacterials within the same drug class, in some circumstances, could be an effective strategy for curbing antibacterial resistance.

Gruson and colleagues[36] observed a reduction in the incidence of VAP after introducing an antibacterial programme that consisted of supervised rotation and restricted use of ceftazidime and ciprofloxacin, which were widely prescribed before the institution of the antibacterial programme. The antibacterial selection was based on monthly reviews of the pathogens isolated from the ICU and their antibacterial susceptibility patterns. Therefore, these clinicians were rotating antibacterial agents based on 'real-time' information, which allowed potentially more effective antibacterials to be prescribed to their patients. They observed a decrease in the incidence of VAP, which was primarily due to a reduction in the number of episodes attributed to potentially resistant Gram-negative bacteria including *P. aeruginosa*, *Burkholderia cepacia*, *S. maltophilia* and *A. baumannii*. These same investigators have now demonstrated that their initial results could be sustained over a 5-year time period.[64]

6. Conclusions

Clinicians caring for patients in the hospital setting must champion and employ strategies for more effective antimicrobial utilisation. The most successful strategies will be multidisciplinary involving co-operation from the pharmacy, nursing staff, treating physicians and infectious disease consultants. Antibacterial utilisation programmes should also be linked to infection control practices in order to minimise the future emergence and spread of antibacterial-resistant microorganisms. The de-escalation approach to antibacterial therapy is a method of providing appropriate initial treatment to patients with serious bacterial infections ('getting it right the first time') while avoiding the unnecessary use of antibacterials in order to prevent the emergence of resistance.

Acknowledgements

This work was supported in part by the Barnes-Jewish Hospital foundation. The author has no conflicts of interest that are directly relevant to the content of this manuscript.

References

1. Goldmann DA, Weinstein RA, Wenzel RP, et al. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals: a challenge to hospital leadership. JAMA 1996; 275: 234-40
2. Gold HS, Moellering RC. Antimicrobial-drug resistance. N Engl J Med 1996; 335: 1445-53
3. Shlaes DM, Gerding DN, John Jr JF, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Clin Infect Dis 1997; 25: 584-99
4. Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe: results of the European Prevalence of Infection in Intensive Care (EPIC) study. EPIC International Advisory Committee. JAMA 1995; 274: 639-44
5. Richards MJ, Edwards JR, Culver DH, et al. Nosocomial infections in medical intensive care units in the United States: National Nosocomial Infections Surveillance System. Crit Care Med 1999; 27: 887-92
6. Quinn JP. Clinical problems posed by multiresistant nonfermenting gram-negative pathogens. Clin Infect Dis 1998; 27 Suppl. 1: S117-24
7. Smith TL, Pearson ML, Wilcox KR, et al. Emergence of vancomycin resistance in *Staphylococcus aureus*. N Engl J Med 1999; 349: 493-501
8. Centers for Disease Control. *Staphylococcus aureus* resistant to vancomycin: United States, 2002. MMWR Morb Mortal Wkly Rep 2002; 51: 565-6
9. Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 1998; 157: 531-9
10. Fridkin SK, Pear SM, Williamson TH, et al. The role of understaffing in central venous catheter-associated bloodstream infections. Infect Control Hosp Epidemiol 1996; 17: 150-8
11. Hardbarth S, Sudre P, Dharan S, et al. Outbreak of *Enterobacter cloacae* related to understaffing, overcrowding, and poor hygiene practices. Infect Control Hosp Epidemiol 1999; 20: 598-603
12. Kollef MH. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. Clin Infect Dis 2000; 31 Suppl. 4: S131-8

13. Kollef MH, Sherman G, Ward S, et al. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999; 115: 462-74
14. Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 2000; 118: 146-55
15. Cosgrove SE, Kaye KS, Eliopoulous GM, et al. Health and economic outcomes of the emergence of third-generation cephalosporin resistance in *Enterobacter* species. Arch Intern Med 2002; 162: 185-90
16. Kollef MH, Ward S. The influence of mini-BAL cultures on patient outcomes: implications for the antibiotic management of ventilator-associated pneumonia. Chest 1998; 113: 412-20
17. Alvarez-Lerma F. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. Intensive Care Med 1996; 22: 387-94
18. Luna CM, Vujacich P, Niederman MS, et al. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest 1997; 111: 676-85
19. Winzer K, Williams P. Quorum sensing and the regulation of virulence gene expression in pathogenic bacteria. Int J Med Microbiol 2001; 291: 131-43
20. Dufour P, Gillet Y, Bes M, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* infections in France: emergence of a single clone that produces Panton-Valentine leukocidin. Clin Infect Dis 2002; 35: 819-24
21. Selvey LA, Whitby M, Johnson B. Nosocomial methicillin-resistant *Staphylococcus aureus* bacteremia: is it any worse than nosocomial methicillin-sensitive *Staphylococcus aureus* bacteremia? Infect Control Hosp Epidemiol 2000; 21: 645-8
22. Hauser AR, Cobb E, Bodi M, et al. Type III protein secretion is associated with poor clinical outcomes in patients with ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*. Crit Care Med 2002; 30: 521-8
23. Roy-Burman A, Savel RH, Racine S, et al. Type III protein secretion is associated with death in lower respiratory and systemic *Pseudomonas aeruginosa* infections. J Infect Dis 2001; 183: 1767-74
24. Leibovici L, Shraga I, Drucker M, et al. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med 1998; 244: 379-86
25. Chow JW, Fine MJ, Shlaes DM, et al. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med 1991; 115: 585-90
26. Morin CA, Hadler JL. Population-based incidence and characteristics of community-onset *Staphylococcus aureus* infections with bacteremia in 4 metropolitan Connecticut areas, 1998. J Infect Dis 2001; 184: 1029-34
27. Carmeli Y, Troillet N, Karchmer AW, et al. Health and economic outcomes of antibiotic resistance in *Pseudomonas aeruginosa*. Arch Intern Med 1999; 159: 1127-32
28. Webb M, Riley LW, Roberts RB. Cost of hospitalization for and risk factors associated with vancomycin-resistant *Enterococcus faecium* infection and colonization. Clin Infect Dis 2001; 33: 445-52
29. Howard D, Cordell R, McGowan Jr JE, et al. Workshop Group: measuring the economic costs of antimicrobial resistance in hospital settings. Summary of the Centers for Disease Control and Prevention-Emory Workshop. Clin Infect Dis 2001; 33: 1573-8
30. Niederman MS. Appropriate use of antimicrobial agents: challenges and strategies for improvement. Crit Care Med 2003; 31: 608-16
31. Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. Ann Intern Med 2001; 134: 298-314
32. Hoffken G, Neiderman MS. Nosocomial pneumonia: the importance of a de-escalation strategy for antibiotic treatment of pneumonia in the ICU. Chest 2002; 122: 2183-96
33. Kollef MH. Hospital-acquired pneumonia and de-escalation of antimicrobial treatment. Crit Care Med 2001; 29: 1473-5
34. Rello J, Sa-Borges M, Correa H, et al. Variations in etiology of ventilator-associated pneumonia across four treatment sites. Am J Respir Crit Care Med 1999; 160: 608-13
35. Namias N, Samiian L, Nino D, et al. Incidence and susceptibility of pathogenic bacteria vary between intensive care units within a single hospital: implications for empiric antibiotic strategies. J Trauma 2000; 49: 638-45
36. Gruson D, Hibert G, Vargas F, et al. Rotation and restricted use of antibiotics in a medical intensive care unit: impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant gram-negative bacteria. Am J Respir Crit Care Med 2000; 162: 837-43
37. Ibrahim EH, Ward S, Sherman G, et al. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. Crit Care Med 2001; 29: 1109-15
38. Friedman ND, Kaye KS, Stout JE, et al. Health-care associated bloodstream infection in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002; 137: 791-7
39. Gaynes R. Health-care associated bloodstream infections: a change in thinking. Ann Intern Med 2002; 137: 850-1
40. Mylotte JM. Nursing home-acquired pneumonia. Clin Infect Dis 2002; 35: 1205-11
41. Hutt E, Kramer AM. Evidence-based guidelines for management of nursing home-acquired pneumonia. J Fam Pract 2002; 51: 709-16
42. American Thoracic Society. Hospital-acquired pneumonia: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies; a consensus statement, American Thoracic Society, November 1995. Am J Respir Crit Care Med 1996; 153: 1711-25
43. Rello J, Ollendorf DA, Oster G, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 2002; 122: 2115-21
44. Siegman-Igra Y, Ravona R, Primerman H, et al. *Pseudomonas aeruginosa* bacteremia: an analysis of 123 episodes, with particular emphasis on the effect of antibiotic therapy. Int J Infect Dis 1998; 2: 211-5
45. Leibovici L, Paul M, Poznanski O, et al. Monotherapy versus beta-lactam-aminoglycoside combination treatment for gram-negative bacteremia: a prospective, observational study. Antimicrob Agents Chemother 1997; 41: 1127-33

46. Fink MP, Snydman DR, Niederman MS, et al. Treatment of severe pneumonia in hospitalized patients: results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastin: the Severe Pneumonia Study Group. Antimicrob Agents Chemother 1994; 38: 547-57

47. Cometta A, Baumgartner JD, Lew D, et al. Prospective randomized comparison of imipenem monotherapy with imipenem plus netilmicin for treatment of severe infections in nonneutropenic patients. Antimicrob Agents Chemother 1994; 38: 1309-13

48. Sieger B, Berman SJ, Geckler RW, et al. Empiric treatment of hospital-acquired lower respiratory tract infections with meropenem or ceftazidime with tobramycin: a randomized study. Crit Care Med 1997; 25: 1663-70

49. Iregui M, Ward S, Sherman G, et al. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 2002; 122: 262-8

50. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar AE, et al. Impact of the outcome of adequate empirical antibiotherapy in patients admitted to the ICU for sepsis. Crit Care Med. In press

51. Leone M, Bourgoin A, Cambon S, et al. Empirical antimicrobial therapy of septic shock patients: adequacy and impact on outcome. Crit Care Med 2003; 31: 462-7

52. Evans RS, Classen DC, Pestotnik SL, et al. Improving empiric antibiotic selection using computer decision support. Arch Intern Med 1994; 154: 878-84

53. Evans RS, Pestotnik SL, Classen DC, et al. A computer-assisted management program for antibiotics and other antiinfective agents. N Engl J Med 1998; 338: 232-8

54. Bailey TC, Ritchie DJ, McMullin ST, et al. A randomized, prospective evaluation of an interventional program to discontinue intravenous antibiotics at two tertiary care teaching institutions. Pharmacotherapy 1997; 17: 277-81

55. Leibovici L, Gitelman V, Yehezkelli Y, et al. Improving empirical antibiotic treatment: prospective, nonintervention testing of a decision support system. J Intern Med 1997; 242: 395-400

56. Singh N, Rogers P, Atwood CW, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit: a proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 2000; 162: 505-11

57. Dennesen PJ, van der Ven AJ, Kessels AG, et al. Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. Am J Respir Crit Care Med 2001; 163: 1371-5

58. Chastre J, Wolff M, Fagon JY, et al. Comparison of two durations of antibiotic therapy to treat ventilator-associated pneumonia (VAP) [abstract]. Am J Respir Crit Care Med 2003; 167: A21

59. Rahal JJ, Urban C, Horn D, et al. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial Klebsiella. JAMA 1998; 280: 1233-7

60. Kollef MH, Vlasnik J, Sharpless L, et al. Scheduled change of antibiotic classes: a strategy to decrease the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med 1997; 156: 1040-8

61. Kollef MH, Ward S, Sherman G, et al. Inadequate treatment of nosocomial infections is associated with certain antibiotic choices. Crit Care Med 2000; 28: 3456-64

62. Kollef MH. Is there a role for antibiotic cycling in the intensive care unit? Crit Care Med 2001; 29 (4 Suppl.): N135-42

63. Gerding DN, Larson TA, Hughes RA, et al. Aminoglycoside resistance and aminoglycoside usage: ten years of experience in one hospital. Antimicrob Agents Chemother 1991; 35: 1284-90

64. Gruson D, Hilbert G, Vargas F, et al. Strategy of antibiotic rotation: long term effect on the incidence and the susceptibilities of gram-negative bacilli responsible for ventilator-associated pneumonia. Crit Care Med 2003; 31: 1908-14

Correspondence and offprints: Dr *Marin H. Kollef*, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8052, St Louis, MO 63110, USA.
E-mail: kollefm@msnotes.wustl.edu