Curbing Resistance Development: Maximizing the Utility of Available Agents

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ABSTRACT

BACKGROUND: Ventilator-associated pneumonia (VAP) in hospital intensive care units (ICUs) is associated with high morbidity and mortality. Effective treatment of VAP can be challenging due to a high prevalence of *Pseudomonas aeruginosa* and multidrug-resistant (MDR) pathogens as causative organisms.

OBJECTIVE: To present the etiology of VAP in the United States (including national resistance trends of common nosocomial pathogens) and review dosing strategies aimed to optimize pharmacokinetic-pharmacodynamic parameters of antimicrobial agents.

SUMMARY: The majority of nosocomial pneumonia cases are caused by gram-negative pathogens, most commonly *P. aeruginosa, Enterobacter* spp., *A. baumannii,* and *K. pneumoniae. S. aureus* is the most common gram-positive pathogen, with 55% of VAP isolates exhibiting methicillin resistance. Combination therapy is recommended when MDR pathogens and *P. aeruginosa* are suspected, although short-course therapy and de-escalation should be considered when appropriate to reduce the risk of resistance. Optimized dosing strategies are important in increasing the probability of achieving successful outcomes. For example, when administering intravenous β-lactam therapy, prolonged infusion can be effective in increasing the T > MIC.

CONCLUSION: Clinicians need to be familiar with local antibiograms as well as regional resistance trends in order to choose appropriate therapy for VAP. Optimized dosing strategies can be effective in increasing the probability of attaining pharmacokinetic-pharmacodynamic targets predictive of successful clinical outcomes.

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DISCLOSURES

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Off-Label Disclosure Statement

In this article, the following off-label use of an antimicrobial agent is discussed: doripenem for the treatment of ventilator-associated pneumonia.

Introduction

Ventilator-associated pneumonia (VAP) is among the most common nosocomial infections originating in the intensive care unit (ICU), affecting 9% to 27% of all intubated patients.[1,2] The attributable mortality can be as high as 33% to 50%.[1,2] The risk of VAP is correlated to the length of stay (LOS) in the hospital or ICU as well as to the duration of mechanical ventilation.[2] *Pseudomonas aeruginosa* and multidrug-resistant (MDR) organisms account for over 20% of VAP infections, with higher rates observed in those with prolonged hospitalization.[3] Infection by these problematic pathogens is associated with increased mortality, duration of mechanical ventilation, and hospital LOS.[3] Therefore, when managing patients at high risk for VAP, it is important to recognize the local epidemiology and resistance trends in order to select the most appropriate initial antimicrobial therapy.

Etiology of Hospital-Acquired Pneumonia

Surveillance data from the National Healthcare Safety Network (NHSN, formerly the National Nosocomial Infections Surveillance System) have shown that gram-negative pathogens are the predominant cause of nosocomial pneumonia, accounting for approximately 70% of infections.[4] Among the infections caused by gram-negative pathogens, *P. aeruginosa* is the leading cause (accounting for approximately 20%) followed by *Enterobacter* spp., *Klebsiella pneumoniae,* and *Acinetobacter baumannii.*[4] The proportion of infections due to *Acinetobacter* has nearly doubled over the past 2 decades (from 4% in 1986 to 7% in 2003). However, there has been a gradual trend of increasing infections due to gram-positive pathogens, mainly *Staphylococcus aureus.*

The etiology of VAP can vary based on (a) local epidemiological trends as well as (b) the timing of onset of infection. According to the 2006–2007 NHSN data, the most common pathogen associated with VAP is *S. aureus* (24.4%) followed by *P. aeruginosa* (16.3%), *Enterobacter* spp. (8.4%), *A. baumannii* (8.4%), and *K. pneumoniae* (7.5%) (Table 1).[5] The time of onset is also an important predictor of causative pathogens. Early-onset VAP, defined as VAP occurring within the first 5 days of hospitalization, is caused by enteric gram-negative bacteria (including *Escherichia coli, K. pneumoniae,* and *Enterobacter* spp.), *Haemophilus influenzae, Streptococcus pneumoniae,* and methicillin-susceptible *S. aureus* (MSSA).[2,6] Late-onset VAP, defined as VAP occurring after 5 days of hospitalization, is more likely to be caused by MDR pathogens,[2,6] including those associated with early-onset VAP as well as *P. aeruginosa* and *A. baumannii*. The variety and complexity of pathogens associated with VAP make choosing an appropriate initial therapy challenging.

Appropriate Antimicrobial Therapy for VAP

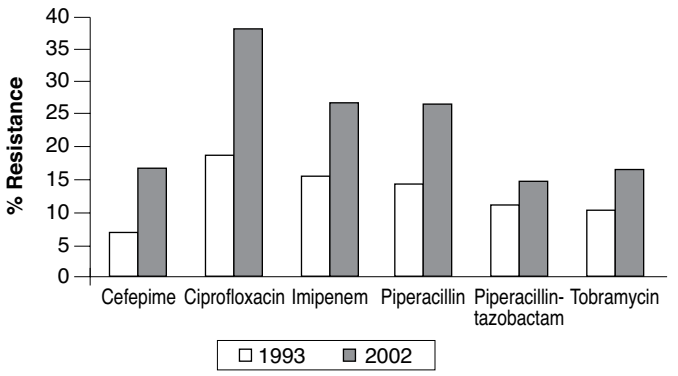
The American Thoracic Society (ATS) and the Infectious Diseases

TABLE 1 Pathogens Associated With VAP, NHSN Data 2006-2007

Species	Isolates (%) (n = 5,960)
S. aureus	24.4
P. aeruginosa	16.3
Enterobacter spp.	8.4
A. baumannii	8.4
K. pneumoniae	7.5
E. coli	4.6

Source: Hidron AI, et al. Infect Control Hosp Epidemiol. 2008;29(11):996-1011.[5]

FIGURE 1 *P. aeruginosa* Resistance in U.S. ICUs



Source: Obritsch MD, et al.Antimicrob Agents Chemother. 2004;48(12):4606-10.[11]

Society of America (IDSA) guidelines on the management of VAP released in 2005 recommend combination therapy for late-onset infections or when *P. aeruginosa, A. baumannii,* or an MDR pathogen is suspected.[2] Gram-negative coverage should include an antipseudomonal cephalosporin or an antipseudomonal carbapenem or an antipseudomonal β-lactam/β-lactamase inhibitor. In addition, an antipseudomonal fluoroquinolone or an aminoglycoside is recommended to ensure adequate coverage. If methicillin-resistant *Staphylococcus aureus* (MRSA) is also suspected, the regimen should include either vancomycin or linezolid.

The appropriate selection of specific agents depends on local susceptibility trends. Therefore, it is critical to be familiar with the antibiogram of the institution as well as specific hospital wards. As discussed earlier, national surveillance data indicate a predominance of *S. aureus* as causative pathogen for VAP.[5] Moreover, MRSA now accounts for nearly 55% of all *S. aureus* VAP isolates. This is important, as MRSA infections are associated with increased mortality, LOS, and hospital costs as compared with MSSA infections.[7-9]

Among the gram-negative pathogens, the most concerning are MDR *P. aeruginosa*, carbapenem-resistant *Acinetobacter* spp., and third-generation cephalosporin-resistant *E. coli* and *Klebsiella* spp.[10] *P. aeruginosa* exhibits elevated rates of resistance to fluoroquinolones and carbapenems and has been trending toward greater resistance to other antimicrobial classes (Figure 1).[11] Over one-third of *Acinetobacter* isolates from VAP patients exhibit resistance to carbapenems—moreover, carbapenem-resistant isolates typically exhibit resistance to multiple antimicrobial classes.[5] MDR *Acinetobacter* isolates commonly have low susceptibility rates to fluoroquinolones, aminoglycosides, and β-lactams, including carbapenems.[12] Therefore, for infections due to *Pseudomonas* or *Acinetobacter*, it is particularly important to know the local antibiogram in order to select the most appropriate combination of agents.

Recommendations for treating infections due to *Acinetobacter* range from the use of combination therapy with an antipseudomonal β-lactam plus an aminoglycoside to combination therapy with colistin plus 1 or more other agents.[13] The resurgence in the use of colistin in hospitals is likely the result of the increased prevalence of *Acinetobacter* infections and a lack of other effective agents. It is important to note that colistin should not be used as monotherapy, since resistance to this agent can occur frequently when used alone.[14,15]

The prevalence of extended-spectrum β-lactamase (ESBL)-producing gram-negative *E. coli* and *K. pneumoniae* has increased in the past several years (Figure 2).[4] These bacteria are resistant not only to third-generation cephalosporins but to other classes of antibiotics as well.[16] ESBL production can be conferred chromosomally or via a plasmid—plasmid-mediated resistance often carries resistance to aminoglycosides and other drug classes as well.[2] Therefore, when treating infections due to ESBL-producing *E. coli* and *K. pneumoniae*, cephalosporins, including fourth-generation cephalosporins, should not be given as monotherapy. There is also a high likelihood of resistance to fluoroquinolones and aminoglycosides.[17] These strains are usually susceptible to carbapenems, which are, therefore, the preferred class for treating these infections. Extensive clinical experience also supports the use of carbapenems for these infections.[2,17] However, it is important to note that multiple mechanisms for resistance to carbapenems have been identified and the prevalence of resistant strains should be carefully monitored.[18]

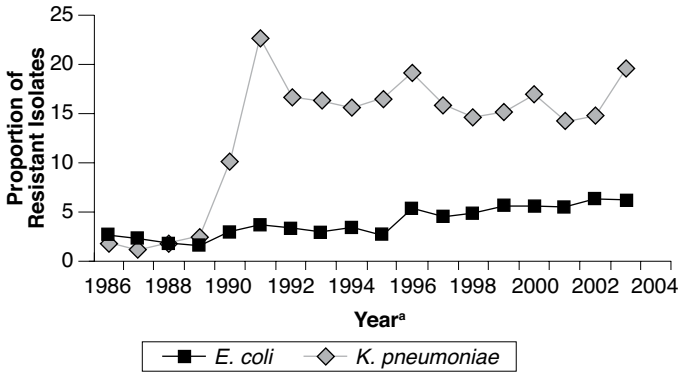
Treatment Strategies to Minimize Resistance Development

Hospital infections will be more challenging given the rising resistance rates observed in nosocomial pathogens coupled with the lack of antimicrobial agents in development targeting these pathogens.[10] Therefore, the available agents must be used judiciously and effectively to reduce the risk of further development of resistance. Treatment strategies that may reduce the further development of resistance, while achieving similar clinical outcomes, include short-course therapy and de-escalation or streamlining therapy.

A prospective, multicenter, randomized study by Chastre et al. compared 8 days (n = 197) with 15 days (n = 204) of appropriate initial therapy for VAP.[19] After 28 days, there were no significant differences in mortality (18.8% for 8-day vs. 17.2% for 15-day treatment groups; treatment difference = 1.6%; 90% CI = –3.7% to 6.9%) or recurrence rates (28.9% for 8-day vs. 26.0% for 15-day treatment; treatment difference = 2.9%; 90% CI = –3.2% to 9.1%) between the 2 treatment groups. Patients receiving the short-course regimen had significantly more antibiotic-free days ($P < 0.001$). However, for patients with infections caused by nonfermenting gram-negative bacteria, including *P. aeruginosa*, short-course therapy resulted in higher rates of pulmonary infection recurrence (40.6% vs. 25.4%, treatment difference = 15.2%; 90% CI = 3.9% to 26.6%). Short-course therapy, therefore, may be appropriate for VAP, except in cases involving nonfermenting gram-negative bacteria.

As mentioned earlier, when *P. aeruginosa* or MDR pathogens are suspected, initial combination therapy increases the probability of providing adequate coverage. However, once the culture and susceptibility results are available and the patient shows signs of improvement, de-escalation of therapy to narrow coverage to only what is necessary should be considered. This is appropriate if an anticipated organism (such as MRSA, *P. aeruginosa*, or *Acinetobacter* spp.) was not recovered or if the organism was susceptible to a more narrow-spectrum agent than initially used.[2] By decreasing total antimicrobial usage, de-escalation of therapy can potentially reduce the risk of emergence of resistance to agents that are no longer deemed necessary for clinical success.

FIGURE 2 Resistance of Nosocomial Isolates to 3rd-Generation Cephalosporins: Nosocomial Infections Surveillance System, 1986–2003



Source: Gaynes R, et al.Clin Infect Dis. 2005;41(6):848-54.[4]
[a]Proportions of K. pneumoniae and E. coli that were resistant were significantly higher in 2003 compared with 1986 ($P < 0.001$ for both, by the Cochran-Armitage χ^2 test for trend).

Optimizing Pharmacokinetic-Pharmacodynamic Parameters

The main goals of antimicrobial therapy are to maximize efficacy while minimizing the development of resistance. Strategies that can help achieve these goals include antimicrobial stewardship, infection control, and optimizing pharmacokinetic/pharmacodynamic (PK/PD) parameters.

This review will not discuss antimicrobial stewardship or infection control tactics. A number of publications provide a thorough understanding of the benefits of antimicrobial stewardship.[20-22] The recent guidelines released by the IDSA and the Society for Healthcare Epidemiology of America (SHEA) state the importance of the clinical pharmacist in implementing an antimicrobial stewardship program at institutions.[20] Infection control is traditionally not the focus of clinical pharmacists, but given the new mandates affecting reimbursement for hospital-acquired infections (HAIs) and heightened efforts to reduce HAIs, all health care personnel should be aware of infection control tactics. The SHEA and IDSA recently released a compendium of strategies to prevent various health care-associated infections in acute care hospitals that can be a valuable resource for hospital-based clinicians.[23]

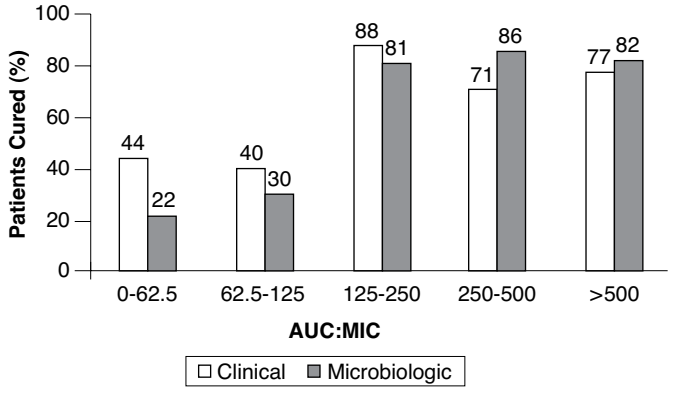
This review will focus on optimizing PK/PD parameters. Antimicrobial agents can be divided into those that exhibit concentration-dependent bacterial killing or time-dependent bacterial killing.

For concentration-dependent agents, the PK/PD parameters predictive of successful clinical outcomes include the peak to minimum inhibitory concentration (MIC) ratio (C_{max}:MIC for aminoglycosides) or the area under the concentration-time curve (AUC:MIC for fluoroquinolones). This was illustrated in a pivotal study by Forrest et al. who evaluated the clinical and microbiologic success rates in nosocomial pneumonia patients based on drug exposure following fluoroquinolone therapy.[24] For patients with an AUC:MIC ratio below 125, microbiologic success rates were consistently below 40% (Figure 3). For those with an AUC:MIC ratio above 125, microbiologic success rates were greater than 80%. It is important to recognize that meeting the PK/PD target does not necessarily guarantee a successful outcome but only predicts a greater chance of clinical success. Patient and pathogen factors can also impact the probability of a successful outcome.

For time-dependent agents such as the β-lactams, the PK/PD parameter predictive of clinical success is the time above the MIC (T > MIC). The T > MIC required for clinical success can vary depending on the particular antimicrobial class.[25] The carbapenems require a T > MIC of 40% for maximal effect while the cephalosporins require T > MIC of 60% to 70%.[25] This variation among the classes can reflect differences in their bactericidal activity as well as the post-antibiotic effect of the agents.

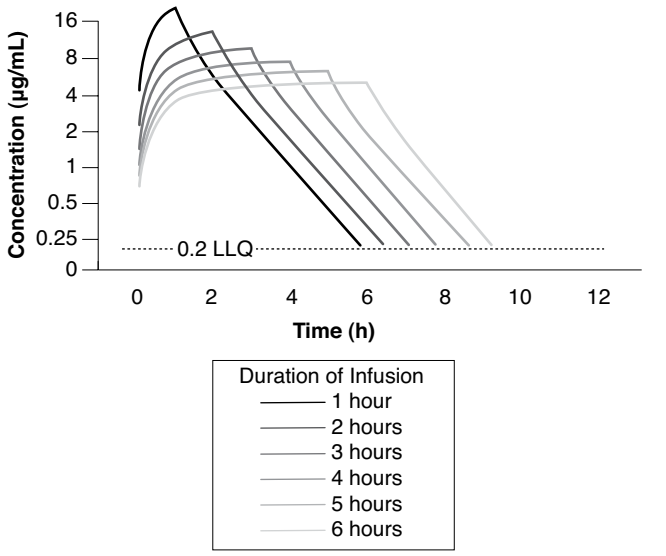
When using intravenous β-lactam therapy, extending the

FIGURE 3 Fluoroquinolone Therapy for Nosocomial Pneumonia: Correlation Between Drug Exposure and Clinical Outcome



Source: Forrest A, et al.Antimicrob Agents Chemother. 1993;37(5):1073-81.[24]

FIGURE 4 PK/PD Profile of Doripenem 500 mg



Republished with permission from Bhavnani SM, Hammel JP, Cirincione BB, Wilker MA, Ambrose PG. Use of pharmacokinetic-pharmacodynamic target attainment analyses to support phase 2 and 3 dosing strategies for doripenem. Antimicrob Agents Chemother. 2005;49(9):3944-47;[28] *published by American Society for Microbiology; Copyright © 2005 American Society for Microbiology. LLQ = lower limit of quantification; PK/PD = pharmacokinetic-pharmacodynamic.*

infusion period can be used to increase the T>MIC and lower the peak concentration.[26,27] The infusion period can be extended through either (a) continuous infusion (i.e., administering a loading dose and then a pump to administer the total daily intravenous dose over a 24-hour period), or (b) prolonged infusion (i.e., administering the same dose and dosing interval but increasing the duration of infusion, such as from 30 minutes to 3 hours).

The use of prolonged infusion has been studied extensively with doripenem. In 1 study, the concentration-time profiles of a 500 mg dose were compared with various infusion times ranging from 1 hour to 6 hours (Figure 4).[28] The impact of longer infusion times were then evaluated by determining the probability of meeting the T>MIC target of 40%. For pathogens with an MIC of 1 µg/mL, 1-hour and 3-hour infusions were effective in meeting the PK/PD target. However, for pathogens with an MIC of 2 µg/mL, a 1-hour infusion had a 77% probability of meeting the PK/PD target compared a 100% probability with a 3-hour infusion. For pathogens with an MIC of 4 µg/mL, a 5-hour infusion was required to achieve a 99% probability of meeting the PK/PD target.

The PK/PD study with doripenem was instrumental in designing a clinical trial comparing doripenem with imipenem for the treatment of VAP.[29] Doripenem (500 mg every 8 hours; n=264) was administered via a 4-hour infusion and compared with an imipenem treatment (500 mg every 6 hours via a 30-minute infusion or 1,000 mg every 8 hours via a 60-minute infusion; n=267). In the clinically evaluable population, there was no significant difference in overall clinical success between the 2 treatment groups (68.3% for doripenem vs. 64.8% for imipenem; treatment difference=3.5%; 95% CI=–9.1% to 16.1%). However, patients treated with doripenem had higher success rates for infections caused by *P. aeruginosa* (80.0% vs. 42.9%) and *K. pneumoniae* (66.7% vs. 50.0%), although neither difference was statistically significant. Such studies illustrate the significance of applying pharmacokinetics-pharmacodynamics when choosing optimal dosing strategies to achieve clinical success.

Pharmacokinetics-pharmacodynamics can also be important in selecting dosing strategies to suppress the development of resistance. A study by Tam et al. used an in vitro model to determine the dosing regimen of meropenem that suppresses development of resistance by *P. aeruginosa*.[30,31] In experiments with a wild-type strain, a large reduction in bacterial burden was observed within the first 24 hours of each regimen tested, although substantial regrowth occurred after 3 days for regimens that maintained T>MIC of 100% and had a C_{min}:MIC of 1.7. Suppression of resistant subpopulations required T>MIC of 100% and a C_{min}:MIC ratio of 6.2 or greater. Achieving these levels would be impractical in a clinical setting, which illustrates the difficulty in suppressing the development of resistance for this problematic pathogen. Lower concentrations of meropenem and the addition of tobramycin was effective in suppressing the development of resistance, confirming the importance of combination therapy for patients suspected with infections by *P. aeruginosa*.

Summary

VAP caused by *P. aeruginosa* and MDR pathogens presents a challenge to clinicians when selecting appropriate initial antimicrobial therapy. Current recommendations point to combination therapy to ensure adequate coverage of potential pathogens followed by de-escalation of therapy once culture and susceptibility results become available. Given the dearth of new antimicrobial agents in the pipeline, de-escalation of therapy can be critical in reducing the potential for development of resistance against available agents and prolonging their effectiveness. Optimized dosing strategies that take into account PK/PD parameters can also be important in increasing the probability of successful outcomes as well as in reducing the risk of development of resistance. Certain tactics, such as prolonged infusion of β-lactam agents, can improve the probability of PK/PD target attainment, although this does not necessarily guarantee a successful outcome.

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