Optimizing Antibiotic Pharmacodynamics in Hospital-acquired and Ventilator-acquired Bacterial Pneumonia

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- Hospital-acquired pneumonia
- Ventilator-acquired pneumonia • Pharmacodynamics
- Monte Carlo simulation

Nosocomial pneumonia, the second most common type of hospital-acquired infection in the United States, can be further classified by when and where it was acquired.[1–3] The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) define hospital-acquired bacterial pneumonia (HABP) as the presence of an acute infection with clinical signs and symptoms in a patient hospitalized for more than 48 hours or within 7 days after discharge from the hospital.[1] Ventilator-acquired bacterial pneumonia (VABP) can be defined by patients ventilated for 48 hours or more or who have been extubated for less than 48 hours and display clinical symptoms.[1] The incidence of nosocomial pneumonia is approximately 5 to 10 cases per 1000 hospital admissions, represents approximately 25% of all infections in intensive care units (ICUs), and increases in frequency in patients who have prolonged intubation periods.[1,4,5] The development of HABP/VABP is associated with an attributable mortality of 33% to 50% and further increases the length of hospital stay by 7 to 9 days and adds greater than $40,000 in excess cost to each patient's cost of care.[1,4–6] This is particularly true for those patients with late-onset symptoms, 5 days or more from admission into the hospital. Along with community-acquired bacterial pneumonia (CABP), HABP/VABP accounts for a substantial burden on health care use and approximately $10 billion in health care cost.[7]

The ATS and the IDSA have supported recommendations for specific antimicrobials and dosing regimens based on infecting organism and risk of multidrug resistant (MDR) organisms but also recognize there is a consistent period of 48 to 72 hours in which therapy is empiric. As such, the ATS and IDSA have also provided recommendations for empiric selection of agents to be used before knowing the pathogen or susceptibility.

An understanding of local epidemiology is necessary to create appropriate empiric regimens. The guidelines use risk stratification to determine which pathogen is most likely. Risk factors include prior receipt of antibiotics and onset of disease in relation to length of hospitalization, among others.[1] Those patients with risk factors have

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a higher likelihood of an infection caused by MDR organisms including *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter* spp, and drug resistant Enterobacteriaceae. For those patients without such risk factors, less drug resistant organisms such as *Streptococcus pneumoniae*, methicillin-susceptible *S aureus*, *Haemophilus influenzae*, and drug-susceptible Enterobacteriaceae are more commonly implicated, although resistant organisms are still possible.[8–10] Surveillance studies routinely report the top pathogens. **Table 1** shows the pathogens isolated from patients hospitalized in the last 5 years of the SENTRY Antimicrobial Surveillance Program.[10] *P aeruginosa* and *S aureus* are the 2 most common pathogens isolated. Empiric selection should be based on institution-specific or even unit-specific information whenever possible and should cover for these common organisms. This approach allows for the greatest likelihood of providing appropriate antibiotic therapy early and then de-escalation once the infecting organism and susceptibility are known.

Once identification of the organism has been made, most microbiology laboratories report susceptibility of the organism as susceptible (S), intermediate (I), or resistant (R). Although these categorical interpretations are helpful, they do not always provide clinicians with adequate information to choose appropriate therapy and never guide the best regimen to choose. The question must always be asked, given the high rate of resistance, "What happens when microbiology reports show nothing susceptible?" Combined with S, I, R, minimum inhibitory concentrations (MICs) are particularly useful to interpret the antibiotic's relative potency and provide important information about which dosage regimens are most likely to be successful against a pathogen. This interaction between drug and bug is the basis for antibiotic pharmacodynamics, and allows for the selection of optimal therapy, or antibiotic regimens (dose, infusion time, and interval) selected to obtain the maximal bactericidal exposure.[11] Optimal therapy through the use of pharmacodynamics is an important concept given the high incidence of infection, the rising resistance rates seen especially in critical care areas, and poor outcomes. It also helps a clinician to choose optimal dosing regimens when there are multiple to choose from. This article reviews the concepts of optimal therapy based on pharmacodynamic properties of specific antibiotics for the treatment of HABP/VABP and expands on the role of antibiotic MICs and alternative dosing, including high-dose strategies and extended-infusion intervals given alterations in pharmacokinetic parameters among these critically ill patients.

Table 1
Incidence of pathogens isolated from patients hospitalized with pneumonia in the United States in the last 5 years of the SENTRY Antimicrobial Surveillance Program

Pathogen	Incidence (%) n = 31,346
S aureus	36.3
P aeruginosa	19.7
Klebsiella spp	8.5
Enterobacter spp	6.5
Acinetobacter spp	4.8
Escherichia coli	4.6
Serratia spp	4.1
Stenotrophomonas maltophilia	3.1
S pneumoniae	2.5
H influenzae	2.5

Data from Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Clin Infect Dis 2010;51(S1):S81–7.

PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetics describes the change in drug concentration throughout the body over time. Pharmacokinetics can vary in patients with different infections, particularly pneumonia, because many patients are critically ill and admitted to the ICU during treatment.[12] Two pharmacokinetic parameters, clearance (CL) and volume of distribution (V_d), can change substantially in critically ill patients.[13–15] A review by Varghese and colleagues[12] presents an in-depth description of antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill. In general, CL can change rapidly given the fluctuating hemodynamic state and renal function of patients with critical illness.[12,16–19] V_d is often larger, with the likelihood of fluid boluses and capillary leakage. Protein binding can also vary dramatically, given it is an acute-phase reactant, which can affect both CL and V_d.[20] Capillary leakage causes fluid to enter the interstitial space from the intravascular space and large fluid boluses to correct hypotension cause an increase in V_d.[21] Given all of the changing parameters, studies have observed inadequate concentrations of antibiotics during critical illness, necessitating the need for optimal doses in these specific patients.[22,23]

The therapeutic effect of antibiotics (ie, inhibiting growth of and killing bacteria) can qualitatively be described as time dependent or concentration dependent.[13] Quantitatively, 3 predominant pharmacodynamic parameters predict antimicrobial efficacy: the time in which the free concentration of the drug is more than the MIC (*f*T > MIC), the ratio of maximum free drug concentration of drug to the MIC (*f*Cmax/MIC), and a combination of time and concentration known as the ratio of the area under the curve (AUC) to the MIC.[13–15] Among antibiotics commonly used to treat HABP/VABP, β-lactams, oxazolidinones, and vancomycin are the most common time-dependent antibiotics.[14,24–26] Of these, β-lactams follow the *f*T > MIC parameter. AUC/MIC is the best predictor of efficacy for oxazolidinones and vancomycin. Aminoglycosides, fluoroquinolones, and polymixins typically display concentration-dependent killing and are best predicted by the ratio *f*Cmax/MIC.[13,27–29] A strong understanding of pharmacokinetic changes in patients with critical illness and HABP is necessary to understand dosing implications. By using specific pharmacodynamic properties of antibiotics, it is then possible to optimize therapy for patients with HABP/VABP.

OPTIMAL PHARMACODYNAMIC ATTAINMENT

Not all antibiotics are created equal. Among the β-lactams, penicillins, cephalosporins, and carbapenems do not require the same *f*T > MIC for maximal killing efficacy. Penicillins, including piperacillin/tazobactam, require the *f*T > MIC by at least 50% to reach maximal bactericidal activity.[13,14] Cephalosporins require *f*T > MIC of at least 50% to 70%.[13,14] One recent article studied cefepime concentrations in patients infected with *P aeruginosa* to determine the optimal *f*T > MIC.[30] Their results from 56 patients found that, when the *f*T > MIC by at least 60%, microbiological failure was only 36.2% compared with 77.8% when the *f*T > MIC did not reach 60%. Carbapenems have also been shown to have bacteriostatic and bactericidal activity when achieving an *f*T > MIC of 20% and 40%, respectively.

Linezolid and vancomycin are time-dependent antibiotics for which AUC/MIC is the best predictor of efficacy, as mentioned earlier. For linezolid, animal models of infection have demonstrated *f*T > MIC and AUC/MIC as predictors of efficacy.[31] This was correlated with a retrospective pharmacodynamic study done in critically ill patients that also found that AUC/MIC was a better predictor than % *f*T > MIC.[32] Pharmacodynamic parameter breakpoints were identified in lower respiratory tract infections at 99 and, overall, the investigators suggest AUC/MIC values of 80 to 120.[32] Vancomycin has shown predictive efficacy given the AUC/MIC greater than or equal to 400.[33] In one study involving patients with lower respiratory tract infections caused by *S aureus*, clinical improvement and microbiological eradication time were significantly better when the AUC/MIC was greater than or equal to 400, as opposed to less than 400.[34]

Aminoglycosides have maintained impressive activity against Gram-negative organisms over time.[1] As a concentration-dependent antibiotic, the predominant pharmacodynamic property needed for efficacy is C_{max}/MIC.[28,35–37] In one single-center study, it was determined that those patients who received an aminoglycoside dosed to a C_{max}/MIC of greater than or equal to 10 for nosocomial pneumonia within the first 48 hours had a 90% probability of fever resolution and leukocyte reduction by day 7.[38]

Fluoroquinolone pharmacodynamics have been studied extensively in animal models and in humans. Levofloxacin has been studied against *S pneumoniae* in patients. Given a free drug concentration AUC/MIC ratio of greater than 33.7, 100% of patients had microbiological response, compared with only 64% when the ratio of AUC/MIC was less than 33.7.[39] In patients infected with Gram-negative organisms including *P aeruginosa*, a higher AUC/MIC ratio of 125 has been found to be optimal.[40–42] This AUC/MIC ratio of greater than 125 for ciprofloxacin significantly prolonged the time to development of resistance and was shown by Forrest and colleagues[40] to significantly decrease the time to bacterial eradication.[40]

OPTIMIZING ANTIBIOTIC THERAPY

Few data have been published to support specific dosing recommendations in critically ill patients. With a multitude of dosing regimens available for each antibiotic, choosing an appropriate dose can be difficult, let alone optimizing the regimen. Cefepime is recommended to be given as 1 to 2 g intravenously (IV) every 8 to 12 hours for HABP/VABP.[1] With this wide range of dosing schemes, it can be difficult for the clinician to decide. It has been published numerous times, but currently recommended dosing strategies do not achieve appropriate pharmacodynamic properties (*f*T > MIC or *f*Cmax/MIC).[30,43–47] Furthermore, large clinical trials can produce evidence to support specific dosing regimens, but are inherently difficult given the acuity of illness, small patient population, and difficulty of obtaining consent.[48] However, Monte

Carlo simulations produce hypothetical patient simulations given a small set of pharmacokinetic parameters collected in the identified patient population. These simulations produce the probability of target attainment (PTA), the probability that a given dosing regimen will achieve its pharmacodynamic target at a given MIC in a specific patient population. PTAs and cumulative fraction of response (CFR), a representation of the in vivo efficacy of dosing regimens when applied to MIC distribution of selected organisms, can be used to determine optimal regimens given an organism and MIC. The value of Monte Carlo simulations is ideal because multiple regimens can quickly be evaluated instead of conducting large and extremely expensive clinical trials. Large multinational surveillance studies like OPTAMA (Optimizing Pharmacodynamic Target Attainment using the MYSTIC [Meropenem Yearly Susceptibility Test Information Collection] Antibiogram) Program provide insight into common causal organisms for HABP. Using this data set, Monte Carlo simulations of multiple regimens allow for comparison of multiple drug and dosing regimens. **Table 2** summarizes results from 4 recent surveillance studies using Monte Carlo simulations to develop theoretic pharmacodynamic exposures against common pathogens isolated in HABP/VABP.[49–52]

Optimization of time-dependent antibiotics requires the concentrations of the drug to remain at more than the MIC for longer durations of the dosing interval. Two ways to accomplish this are through extended-infusion and continuous-infusion strategies. Piperacillin-tazobactam dosing regimens were identified using Monte Carlo simulations to predict higher probabilities of target attainment given a range of MICs for *P aeruginosa*.[53] Simulations showed that, when 3.375 g was given as a 4-hour infusion every 8 hours, the probability of reaching optimal target attainment, defined as greater than 90%, was achieved with MICs up to 16 μg/mL. Recommended regimens of 3.375 g IV every 6 hours and 3.375 g IV every 4 hours decreased to less than the optimal target attainment at MICs of 8 μg/mL.

Cefepime dosing regimens have been extensively studied to determine optimal dosing strategies.[22,25,30,44,54] In one study, multiple intermittent-infusion regimens were compared with continuous-infusion regimens using a Monte Carlo simulation based on pharmacokinetic data from 11 patients in ICUs.[55] The simulation found that at the highest dose per day given as an intermittent infusion, 2 g IV every 8 hours, the PTA was greater than 90% up to and including an MIC of 2 μg/mL. Continuous infusion of 6 g cefepime per day was able to achieve PTA up to 8 μg/mL. A continuous infusion of 2 g cefepime per day was able to achieve similar PTA to the intermittent infusion of 2 g IV every 8 hours with optimal PTA at an MIC of 2 μg/mL. This result shows the ability of continuous infusion to be used for more resistant isolates with higher MICs, and the possibility of using less drug to achieve the same PTA.

Similar results can be found for meropenem. The PTA values of meropenem in critically ill patients receiving meropenem were calculated using a 5000-patient Monte Carlo simulation.[56] Multiple regimens were used and are displayed in **Fig. 1**. As the regimen (1 g IV every 8 hours) is manipulated from a 0.5-hour infusion to a 3-hour infusion, the optimal PTA increases from an MIC of 1 μg/mL to 4 μg/mL. Subsequently, higher doses produce even further increases in PTA, with 2 g IV every 8 hours as a 3-hour infusion increasing the PTA from 4 μg/mL for the 1 g IV every 8 hours regimen to 8 μg/mL. By giving higher doses at prolonged infusion times, meropenem exposures would be optimal for an additional 22% of *P aeruginosa* isolates from 214 US hospitals collected from the 2009 CAPITAL (Carbapenem Antimicrobial Pseudomonas Isolate Testing at Regional Locations) Surveillance Program.

As mentioned previously, renal function in patients with critical illness can change dramatically because of poor perfusion to the kidneys. Crandon and colleagues[56] collected pharmacokinetic samples from patients admitted to their ICUs at Hartford Hospital, Hartford, CT, receiving meropenem for at least 3 consecutive doses. A Monte Carlo simulation was then performed to create 5000 concentration-time profiles. Simulations were run for 3 different creatinine clearance (CrCL) ranges including 50 to 120 mL/min, 30 to 49 mL/min, and 10 to 29 mL/min. From these profiles, the PTA assuming a pharmacodynamic target of at least 40% $fT > MIC$ was calculated for a range of MICs from 0.008 μg/mL to 64 μg/mL. Results of selected regimens given as a 0.5-hour and 3-hour infusion are described in **Table 3**. Given worsening renal function with a CrCL of 30 to 49 mL/min, meropenem doses of 1 g every 8 hours as a 0.5-hour or 3-hour infusion were sufficient to target an MIC up to 4 μg/mL; however, only the 3-hour infusion was able to meet optimal conditions at MICs of 8 μg/mL. Doses of 500 mg every 6 hours as a 0.5-hour infusion and 1 g every 12 hours both achieved optimal target attainment ($\geq$95.1% and $\geq$96%, respectively) against MICs greater than or equal to 4 μg/mL. These results show that organisms with high MICs are still able to be treated with meropenem given an optimized dose and most likely the need for extended infusion.

Pharmacodynamic optimization of concentration-dependent antibiotics can be done through increases in doses. Through the use of high-dose, extended-interval dosing, aminoglycosides can achieve high C_{max}/MIC ratios, and can help to decrease the risk of toxicity, most commonly ototoxicity and nehprotoxicity.[35–37] After implementation of a once-daily aminoglycoside program, one study showed continued clinical efficacy and decreased rates of toxicity from a historical perspective.[37] Empiric dosing strategies based on the patient's weight and CrCL have been created. It is important to individualize the dosing regimen by manipulating the dose to increase or decrease the peak concentration and increase or decrease the interval between doses to change the trough concentration to achieve an optimal C_{max}/MIC of greater than or equal to 10. Given the high rate of success and decreased incidence of side effects, high-dose, extended-interval dosing is recommended in the guidelines for HABP/VABP.[1]

Fluoroquinolones are concentration-dependent antibiotics listed in the guidelines for the treatment of HABP in combination with an antipseudomonal β-lactam for patients with risk factors for MDR organisms.[1] Given dose-related toxicity, specifically central nervous system related toxicities, it has been difficult to obtain AUC/MIC ratios greater than 125.[57] One study of levofloxacin conducted in critically ill patients with ventilator-associated pneumonia found that the *f*AUC after being given a 1000-mg loading dose on day 1 and 500 mg daily thereafter was ~50 μg/mL.[58] The investigators concluded, based on their pharmacokinetic results, that a dose of 1000 mg daily would most likely result in treatment failures against pathogens with MICs of 2 μg/mL, pathogens that would be labeled as levofloxacin susceptible in microbiology sensitivity and susceptibility reports. Furthermore, a randomized, double-blind, retrospective study was conducted to determine the safety and efficacy of 2 regimens of levofloxacin for CABP: 500 mg daily for 10 days or 750 mg daily for 5 days.[59] Baseline characteristics between patients were similar, with the 500-mg group being slightly older (76 vs 72.5 years; $P = .029$) and having higher pneumonia severity index (PSI) scores (90.7 vs 83.1; $P = .017$). Results showed no difference between clinical efficacy and microbiological eradication even when controlling for age and PSI scores. The incidence of adverse events was not different either. This study shows the ability to decrease duration of therapy by optimizing therapy. Through the use of higher doses, this concentration-dependent antibiotic was able to be given in a shorter course.

CLINICAL APPLICATIONS OF PHARMACODYNAMIC OPTIMIZATION

Lodise and colleagues[53] adopted an extended-infusion strategy for piperacillin/tazobactam, the most common antipseudomonal β-lactam at their institution. After implementation, the investigators conducted a retrospective cohort study to identify differences between the historical intermittent-infusion group (3.375 g IV every 4–6 hours) and the extended-infusion group (3.375 g IV every 8 hours as a 4-hour infusion). Baseline characteristics between the groups were similar. Those in the historical control group predominately received 3.375 g IV every 6 hours, with only 4 patients (4.3%) receiving more frequent dosing every 4 hours. In those patients with an Acute Physiology and Chronic Health Evaluation (APACHE II) score greater than or equal to 17, 14-day mortality and median length of stay were both lower in patients who received extended-infusion regimens than the intermittent-infusion regimen. In those patients with APACHE II scores less than 17, there was no statistically significant reduction in either mortality or length of stay. This study identified a possible benefit when using extended-infusion piperacillin/tazobactam in critically ill patients with APACHE II scores greater than or equal to 17.

In one retrospective chart review, intermittent-infusion ceftazidime 2 g infused over 30 minutes every 12 hours was compared with continuous-infusion ceftazidime 2 g infused over 12 hours every 12 hours after a loading dose of 1 g over 30 minutes.[60] A total of 121 patients were enrolled, with similar baseline characteristics between groups. After logistic regression analysis, continuous-infusion ceftazidime was associated with a significantly greater clinical cure rate than intermittent infusion, 89.3% versus 52.3% respectively. Another retrospective study was designed to identify differences in clinical cure in patients with VABP between meropenem 1 g IV as a 30-minute infusion every 6 hours versus continuous-infusion meropenem 1 g IV over 6 hours every 6 hours.[61] There were no significant differences at baseline including microbiologic data between groups. Continuous-infusion meropenem showed a significantly better clinical cure rate than intermittent infusion. Against *P aeruginosa*, there was a clinical cure rate of 84.6% versus 40% with the intermittent infusion. When the MIC of the infecting organism was greater than or equal to 0.5, clinical cure was observed significantly more in the continuous-infusion group than with the intermittent infusion, 80.95% versus 29.41%, respectively.

Table 2
Summary of antibiotic drug regimens and cumulative fraction of response against common pathogens isolated in patients with HABP using Monte Carlo simulations from the OPTAMA and PASSPORT programs

	CFR (%)				
Drug and Regimen[a]	***S aureus* (MRSA Excluded)**	***P aeruginosa***	***Klebsiella* spp**	***Acinetobacter* spp**	***E coli***
Cefepime					
1 g IV every 12 h	94.7	76.8–80.9	83.9–99.3	32.3–44.5	90.2–99.9
1 g IV every 8 h	98.1	86.2	88.0	46.3	92.5
1 g IV every 6 h	ND	93.6–94.9	93.7–100	ND	98.8–100
2 g IV every 12 h	98.0	83.6–91.1	90.9–99.8	52.9–65.5	94.4–100
2 g IV every 8 h	99.8	90.1–97.1	95–100	60.9–83.5	96.9–100
2 g IV every 8 h (3-h infusion)	100	93.2–98.0	96.4–100	64.0–82.7	97.7–100
Ceftazidime					
1 g IV every 8 h	83.6	78.8–86.9	72.3–97.2	26.8–53.1	90.1–99.5
2 g IV every 8 h	97.8	91.3–97.9	83.9–98.3	53.4–73.9	97.4–99.8
2 g IV every 8 h (3-h infusion)	99.5	93.3–98.2	92.4–99.8	55.2–80.7	99.1–99.9
Ciprofloxacin					
400 mg IV every 12 h (1-h infusion)	ND	56.1–63.5	79.8–93.6	43.6–44.5	73.2–91.6
400 mg IV every 8 h (1-h infusion)	75.8	61.9–67.0	58.3–95.6	20.8–46.3	46.8–78.6
Doripenem					
500 mg IV every 8 h (1-h infusion)	ND	82.8	96.4	60.3	99.0
500 mg IV every 8 h (4-h infusion)	ND	93.9	ND	67.5	ND
1 g IV every 8 h (1-h infusion)	ND	88.8	ND	66.4	ND
1 g IV every 8 h (4-h infusion)	ND	97.2	ND	72.8	ND
2 g IV every 8 h (1-h infusion)	ND	93.1	ND	73.7	ND
2 g IV every 8 h (4-h infusion)	ND	98.8	ND	80.6	ND

Ertapenem					
1 g IV every 24 h	99.8	14.0	80–97.9	2.9	99.3–99.9
Imipenem					
500 mg IV every 8 h	ND	63.2	91.9	41–60.2	95.5
500 mg IV every 6 h	99.1	61.8–86.3	78.6–99.4	63.7–76.7	97.7–100
1 g IV every 8 h	99.9	66.9–87.7	80.6–99.6	46.3–79.6	99.4–99.8
1 g IV every 8 h (3-h infusion)	100	74.0–93.9	83.6–100	58.2–71.6	100
Levofloxacin					
500 mg IV every 24 h	ND	40.4	90.3	46.7	78.3
750 mg IV every 24 h (1.5-h infusion)	82.3	40.4–55.8	50.2–91.8	18.1–48.2	39.6–78.6
Meropenem					
500 mg IV every 8 h	100	80.7	97.5	59.4	99.8
500 mg IV every 6 h	100	72.9–89.9	81.9–100	37.8–67.4	99.8–100
1 g IV every 8 h	100	76.7–91.7	83.0–100	42.0–70.6	99.9–100
1 g IV every 8 h (3-h infusion)	100	83.3–95	84.8–100	49.1–68.9	100
2 g IV every 8 h	100	86.0–94.9	86.4–100	53.1–69.6	100
2 g IV every 8 h (3-h infusion)	100	93.4–97.0	89.5–100	62.3–74.9	100
Piperacillin/tazobactam					
3.375 g IV every 6 h	ND	74.1–78.3	81.1–93.9	46.6	92.9–97.2
3.375 g IV every 4 h	ND	82.0	95.6	51.9	98.4
3.375 g IV every 8 h (3-h infusion)	ND	80.5–85.1	84.7–96.6	48.3	96.6–98.4
4.5 g IV every 6 h	93.2	76.6–82.0	55.3–95.1	20.1–49.0	78.5–97.6
4.5 g IV every 8 h	ND	69.3–72.5	91.3	44.3	95.2
4.5 g IV every 6 h (3-h infusion)	100	84.1–89.2	60.5–97.2	26.9–52.6	85.2–98.7

Abbreviation: ND, not done.

[a] All infusions are 0.5 hours unless noted.

Data from Refs.[49–52]

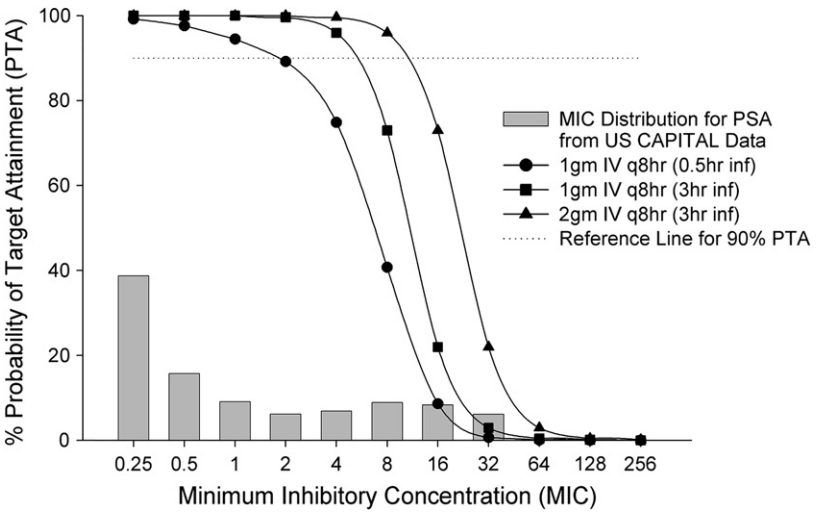

Fig. 1. Probability of attaining 40% *f*T > MIC in doubling dilutions with varying meropenem dosing regimens used for HABP/VABP. The MIC distribution for *P aeruginosa* (PSA) against respiratory isolates collected from the CAPITAL (Carbapenem Antimicrobial Pseudomonas Isolate Testing at Regional Locations) data is plotted to explain the implication of the PTA curves.

Furthermore, Lorente and colleagues[62] conducted a historical cohort study to determine differences between continuous-infusion and intermittent-infusion piperacillin/tazobactam. Results from this study were similar to the 2 previous studies, identifying a statistically higher rate of clinical cure with continuous-infusion piperacillin/tazobactam given as a loading dose of 4.5 g IV over 30 minutes, then 4.5 g IV infused over 6 hours versus 4.5 g IV over 30 minutes every 6 hours. Clinical cure was statistically significant when MICs were 8 μg/mL or greater, with clinical cures for the continuous-infusion regimen equal to ~88%, whereas the intermittent-infusion clinical cure rate was only 40% when the MIC was 8 μg/mL, and even less (16.7%)when the MIC was 16 μg/mL against piperacillin/tazobactam. Mortality, duration of mechanical ventilation, and ICU stay were not statistically significant in this study.

A study published by Nicasio and colleagues[63] created a pharmacodynamic-based clinical pathway for empiric antibiotic choice in patients with

Table 3
PTA of various meropenem regimens at varying degrees of renal function for an MIC range

CrCL Regimen	PTA, % MIC 1 μg/mL	PTA, % MIC 2 μg/mL	PTA, % MIC 4 μg/mL	PTA, % MIC 8 μg/mL	PTA, % MIC 16 μg/mL
50–120 mL/min					
1 g IV every 8 h (0.5-h infusion)	94.5	89.2	74.8	40.7	8.6
1 g IV every 8 h (3-h infusion)	97.6	94.5	89.2	74.8	40.7
2 g IV every 8 h (0.5-h infusion)	100	99.6	99.6	73	21.9
2 g IV every 8 h (3-h infusion)	100	100	99.8	95.9	73.0
30–49 mL/min					
1 g IV every 8 h (0.5-h infusion)	100	100	99.8	89.6	38.4
1 g IV every 8 h (3-h infusion)	100	100	99.8	89.6	38.4
10–29 mL/min					
1 g IV every 12 h (0.5-h infusion)	99.7	98.0	84.0	43.5	11.5
1 g IV every 12 h (3-h infusion)	100	99.9	96.0	61.3	17.6

Data from Crandon JL, Ariano RE, Zelenitsky SA, et al. Optimization of meropenem dosage in the critically ill population based on renal function. Intensive Care Med 2011;37(4):632–38.

VABP. A unique aspect of the development of this study was that the investigators used institution-specific information to develop empiric therapy for each of their ICUs. Monte Carlo simulations were designed and used to calculate the cumulative response given specific antibiotic regimens. In the surgical and neurotrauma ICU, cefepime 2 g IV infused over 3 hours every 8 hours was chosen given its best response rate. In the medical ICU, a meropenem regimen was chosen (2 g IV every 8 hours as a 3-hour infusion). High-dose, extended-interval tobramycin and vancomycin were also added to the empiric regimen. Patients were included in the study if admitted to the ICU and diagnosed with VABP based on clinical and radiologic criteria and compared with a historical control group. Baseline clinical characteristics were similar between groups with the exception of the historical group, which had a higher incidence of liver disease than the clinical pathway (17.6% vs 3.2%).

Triple-drug regimens recommended by the current ATS/IDSA guidelines were used in only 3 (4.1%) patients in the historical control and in 73 (77.7%) of the clinical pathway patients, a statistically significant result ($P<.001$). Combination therapy targeting *P aeruginosa* was also statistically higher in the pathway groups, whereas fluoroquinolone therapy, having some of the lowest cumulative responses against *P aeruginosa* in the Monte Carlo simulation, was lower in this group. Patients treated using the clinical pathway had lower infection-related mortality and more commonly received appropriate antibiotics within 24 hours, an important treatment strategy for sepsis and critically ill patients. Of the 94 patients treated on the clinical pathway, 9 patients had infections with MICs greater than or near the breakpoint. Of the 9 patients treated, 8 of them responded successfully, most with prolonged-infusion regimens. The clinical pathway also showed a lower rate of superinfections and infection-related length of stay. Implementation of the clinical pathway for empiric treatment of VABP, patient outcomes, including infection-related mortality and superinfections, were improved. The investigators not only showed improved patient outcomes but it was later determined that patients on the clinical pathway had shorter lengths of ICU and total hospital stay and lower hospital costs after the treatment of VABP when controlling for the differing baseline demographics and the length of stay before developing VABP.[64] The investigators also mention the increased cost of antibiotic use when giving higher doses and using empiric triple therapy, but this small cost was offset by the large savings associated with decreased duration of antibiotic use and length of hospital stay. The program implemented at Hartford Hospital, Hartford, CT, is the first known clinical pathway to use institution-specific information to choose empiric antibiotic choice and improve patient outcomes in patients with VABP while reducing costs.

SUMMARY

There is a high morbidity and mortality associated with hospital-acquired and ventilator-acquired pneumonia and costs associated with this type of treatment are substantial. Although prevention methods are necessary to decrease the risk and incidence, no program can eliminate these infections. Pharmacodynamic optimization of antibiotics is necessary given the high rates of resistance seen in nosocomial infections. ICUs and critical care units are seeing resistance rates increase to the point of complete resistance against all available antibiotics. Optimizing pharmacodynamics can increase the likelihood of obtaining adequate concentrations to achieve bactericidal concentrations and treat pathogens deemed nonsusceptible by conventional laboratory susceptibility panels. The use of extended-infusion and continuous-infusion strategies with time-dependent antibiotics has been implemented and shown to improve the probability of clinical cure. Furthermore, high-dose, extended-interval strategies have been used to optimize the pharmacodynamic profile while minimizing the potential toxicity of the aminoglycosides.

Specific programs using individual institution data like the one created at Hartford Hospital are ideal given that local and even regional resistance rates can be dramatically different. Enhancing patient outcomes by identifying and using optimal antibiotic therapies through the use of Monte Carlo simulation can be an effective tool in the management of infection. In addition to the noted clinical usefulness and better outcomes associated with this pneumonia pathway, the resulting improvements in the economics of care further support the feasibility of this management strategy.

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