

Comparative Effectiveness Review

Number xx

Pharmacokinetic/Pharmacodynamic Measures for Guiding Antibiotic Treatment for Nosocomial Pneumonia

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Pharmacokinetic/Pharmacodynamic Measures for Guiding Antibiotic Treatment for Nosocomial Pneumonia

Structured Abstract

Objectives: To conduct a systematic review of the use of pharmacokinetic/pharmacodynamic (PK/PD) measures or strategies to dose and monitor intravenous (IV) antibiotics in the treatment of nosocomial pneumonia in hospitalized adults.

Data sources: MEDLINE® (via PubMed), Cochrane Library, International Pharmaceutical Abstracts, and ClinicalTrials.gov from January 1, 2004, to May 15, 2013.

Review methods: Two investigators independently selected, extracted data from, and rated risk of bias of studies. We graded strength of evidence based on established guidance.

Results: Six studies (four trials; two cohort studies) met inclusion criteria. Evidence is insufficient to conclude whether using PK/PD measures to inform decisions about dosing or monitoring IV antibiotic treatment improves intermediate or health outcomes. Only a single study (rated high risk of bias) used PK/PD measures to study the impact of different antibiotic dosing levels on clinical responses, such as time on mechanical ventilation, treatment failure, and mortality.

Evidence is also insufficient to draw conclusions about the effect of continuous infusions of beta-lactam antibiotics compared with the effect of intermittent infusions on outcomes related to clinical response, mechanical ventilation, morbidity, mortality, or rates of antibiotic-related adverse events. Clinical response, duration of mechanical ventilation, superinfection, rates of antibiotic-related adverse events, and infusion-related adverse effects did not differ significantly in any study.

Conclusions: Despite the theoretical advantages of optimizing IV antibiotic dosing using PK/PD principles in patients with nosocomial pneumonia, major gaps in the available evidence preclude our drawing conclusions or explaining clinical or policy implications. The near-absence of strong evidence, particularly related to clinical applications, limits our ability to either support or oppose the adoption of various PK/PD strategies for this specific clinical purpose.

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Executive Summary

Background

Nosocomial Pneumonia: Epidemiology

Hospital-acquired (or nosocomial) pneumonia (HAP) is the second most common hospital-acquired infection, occurring especially in the elderly, immunocompromised patients, surgical patients, and individuals receiving enteral feeding through a nasogastric tube. The incidence rates for HAP, which can occur in all areas of hospitals, range from 5 to more than 20 per 1,000 admissions.^{1,2}

HAP is the leading cause of hospital-acquired infection in the intensive care unit (ICU).¹ Almost one-third of HAP episodes are acquired in ICUs;³ and as many as 90 percent of ICU cases may be ventilator associated.^{3,4} In the ICU setting, HAP accounts for up to 25 percent of all infections and for more than 50 percent of the antibiotics prescribed.¹

Guidelines issued in 2005 by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) provide the following definitions for HAP, ventilator-associated pneumonia (VAP), and health care-associated pneumonia (HCAP):¹

- HAP is a pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission. Clinicians may manage HAP patients in a hospital ward or in an ICU when the illness is more severe. Some patients may require intubation after developing severe HAP; in these cases, clinicians should manage them in ways similar to treating patients with VAP.
- VAP is a pneumonia that presents more than 48 hours after endotracheal intubation. It is a severe type of HAP because of the difficulty in treating it, and its prognosis is poor.⁵
- HCAP is a pneumonia that develops in any patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic.

Unless specified otherwise, the term “HAP” includes VAP and HCAP. Most of the principles of HAP and VAP overlap with those of HCAP.

HAP is most often caused by bacterial pathogens, and it may be polymicrobial. Aerobic Gram-negative bacilli, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* species, are the most common causes of HAP. Cases of infections caused by Gram-positive cocci, including *Staphylococcus aureus* (*S. aureus*), are becoming more common in the United States. HAP caused by *S. aureus* is found with greater frequency in patients with diabetes mellitus, patients with head trauma, and patients hospitalized in ICUs. HAP caused by viral or fungal pathogens is rare in immunocompetent patients.¹

HAP is associated with increased morbidity and mortality, longer lengths of inpatient stays, and higher costs of care despite advances in antimicrobial therapy, supportive care, and prevention. For example, episodes of HAP that are not associated with ventilator use raise both hospital lengths of stay and costs of care; in one report from Asian countries, they were associated with death rates of between 27 percent and 50 percent.²

Patients who have received mechanical ventilation are at the greatest risk for nosocomial pneumonia; intubation increases a patient's HAP risk by 6 to 21 times. Mortality from VAP among patients who have acquired VAP in ICUs can be higher for patients who receive inadequate empirical therapy.¹⁰ Additional costs per episode of VAP may be as high as \$40,000.¹¹

Nosocomial Infection: Treatment

Appropriate antibiotic therapy improves survival significantly for patients with HAP.¹²⁻¹⁵ Relevant antibiotics for treating patients with HAP include broad spectrum beta-lactams, vancomycin, and aminoglycosides, among others. Table A lists antibiotic classes and individual agents that might be used to treat HAP; bold items are those used most often.

Table A. Intravenous antibiotics for which PK/PD measures could be used

Drug Class	Drug^a
Aminoglycosides	Gentamicin Tobramycin Amikacin
Beta-lactams Penicillins	Penicillin G Oxacillin Nafcillin
Beta-lactam/Beta-lactamase inhibitors	Ampicillin/sulbactam Piperacillin/tazobactam Ticarcillin/clavulanic acid
Cephalosporins	Cefazolin Ceftriaxone Cefotaxime Ceftazidime Cefepime Ceftaroline
Monobactams	Aztreonam
Carbapenems	Doripenem Ertapenem Imipenem Meropenem
Fluoroquinolones	Levofloxacin Ciprofloxacin Moxifloxacin
Glycopeptides	Vancomycin
Glycylcyclines	Tigecycline
Oxazolidinone	Linezolid
Polymyxin	Colistin (also called colistimethate sodium)
Rifamycins	Rifampin Rifampicin
Tetracyclines	Doxycycline Minocycline

Optimal treatment involves choosing the right drug or combination of drugs, the proper dose and route of administration, the appropriate duration, and is followed by de-escalation to pathogen-directed therapy.¹ Subtherapeutic dosing of antibiotics has been associated with poorer clinical outcomes and emergence of antibiotic resistance.¹⁶⁻¹⁹

Optimal dosing of antibiotics based on principles of pharmacokinetics and pharmacodynamics (PK/PD) has the potential to improve outcomes and prevent the development of resistance in patients with HAP. PK is the study of the time course of drug absorption,

distribution, metabolism, and excretion. The primary goals of clinical PK include enhancing efficacy and decreasing toxicity of an individual patient's drug therapy. PD refers to the relationship between the concentration of the drug at the site of action and the resulting effect. Antibiotic PD relates PK parameters to the ability of an antibiotic to kill or inhibit growth of bacterial pathogens.²⁰ Antibiotics can be classified based on PD characteristics that affect bacterial killing in relation to the minimum inhibitory concentration (MIC) of the organism.

To improve the effectiveness of the available antibiotics for nosocomial pneumonia, the 2005 ATS/IDSA guidelines recommended considering PK/PD properties when selecting an antibiotic regimen, dosage, and route of administration. The goal of these guidelines is to provide recommendations for the selection of adequate therapy and thereby achieve optimal patient outcomes. Because this antibiotic dosing logic is based on *in vitro* and *in vivo* observations, it may not account for the heterogeneity of patient populations with HAP, the complex pathologic environment in the infected lung, and the drug concentration achieved at the site of the pneumonia. Current antibiotic dosing strategies also do not directly consider the variety of antibiotic-resistance mechanisms in bacteria that contribute to the persistence of HAP. Suboptimal antibiotic concentrations at the site of infection may not eradicate resistant organisms; may in turn lead to treatment failure and/ or contribute to emerging antibiotic resistance.

Concerns in the United States and abroad about the increasing rates of superinfection (i.e., infection with a new organism) and new resistance patterns in pathogens call for strategies to optimize existing antibiotic treatment options for HAP.^{6,7} Antibiotic resistance is a growing and significant threat to public health. The incidence rates of drug resistance among many common HAP pathogens have increased dramatically over the past 3 decades. During the same period of time, the number of new antibiotics developed has decreased. With fewer antibiotic options, ensuring the appropriate and judicious use of these drugs becomes increasingly important.^{8,9} Optimization of antibiotic dosing is important to improve individual patient outcomes; optimal antimicrobial exposure may also serve to prevent the emergence of resistant populations of organisms. Subtherapeutic concentrations of antibiotics may contribute to the emergence or acceleration of resistance. Consequently, any procedures that can help to guide dosing of antibiotics has important implications, not only for the individual patient being treated, but for public health concerns as well.

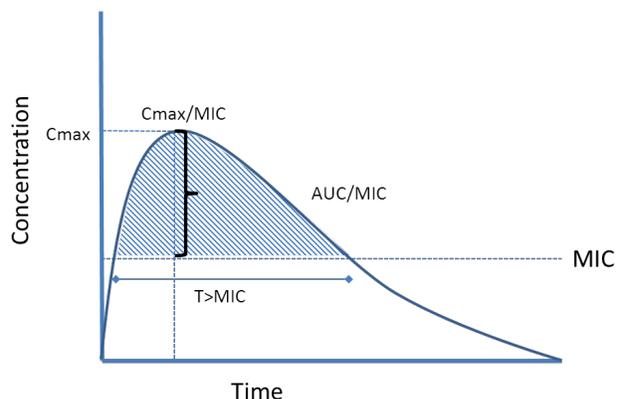
Scope and Key Questions

Scope of This Review

This review aims to document the impact of contemporary approaches to PK/PD-guided dosing of intravenous (IV) antibiotic therapy on clinical outcomes for patients with HAP. In general, antibiotics are grouped into one of three categories based on their mode of bacterial killing: (1) concentration dependent, (2) time dependent, or (3) a combination of concentration and time dependent. These three modes are expressed as ratios to the MIC of the organisms (Figure A).

- Concentration-dependent antibiotic: Peak concentration to MIC (expressed as C_{max}/MIC)
- Time-dependent antibiotic: Time that the serum concentration is greater than the MIC (expressed as $T > MIC$)
- Area under the concentration-time curve (AUC) in relationship to MIC (expressed as AUC/MIC).

Figure A. Ratios related to the minimum inhibitory concentration of the organisms



Abbreviations: AUC = antibiotic area under the concentration-time curve; AUC/MIC = the ratio of the antibiotic area under the curve to the time above the minimum inhibitory concentration needed to inhibit microorganisms; C_{max} = the maximum serum concentration needed to inhibit microorganisms; C_{max}/MIC = ratio of maximum serum concentration (or peak) to the time above the minimum inhibitory concentration needed to inhibit microorganisms; MIC = minimum inhibitory concentration; T = time.

Given the PK/PD properties of antibiotics, clinicians can optimize the PD effects of antibiotics by making decisions about dosing strategies. For example, to optimize the PD effect of a concentration-dependent antibiotic, clinicians may choose to increase the dose, resulting in a higher C_{max}/MIC ratio.

Populations of interest for this review included adults who have presumed or confirmed HAP, VAP, or HCAP and who are being treated with IV antibiotic treatment. We looked at benefits defined as both intermediate outcomes (clinical response; use of ventilators) and health outcomes (morbidity and mortality); we also examined evidence about adverse events (harms). We examined evidence relating to nosocomial pneumonia that begins in the hospital setting (e.g., emergency department, floor, or ICU) and relating to treatment that continues in other settings; we also included studies of patients who acquired nosocomial pneumonia in a nursing home setting.

This review is relevant to several dilemmas that clinicians face about how best to select doses and to monitor the use of IV antibiotics for these severely ill patients while taking account of the various PD properties that different IV antibiotics have various patient-specific factors, and resistance patterns of the pathogens. Of concern are both presumed benefits and harms of using PK/PD measures for these purposes. It also attempts to address one specific question concerning the beta-lactam class of antibiotics. Finally, we examine what may be known about how outcomes (benefits or harms) relate to patient populations characterized by sociodemographic or clinical characteristics.

We excluded studies of fungal pneumonia in this review, because fungal infections would involve a different set of PICOTS from those found in the literature for bacterial infections. Because the report scope was limited to HAP, VAP, or HCAP, we also excluded studies of community-acquired pneumonia and of other pneumonias in which treatment began in a setting other than the hospital (or nursing home). In addition, because of the report's focus on pneumonia, we did not include studies of shock, sepsis, or other infections that did not provide data for nosocomial pneumonia patients. Finally, we excluded studies in which serum concentration had been measured without comparing different serum concentration targets, because this type of intervention would be considered standard of care and is not a study design that is looking at optimization of PK/PD measures to inform treatment decisions.

Key Questions

We addressed three key questions (KQs). The analytic framework used to guide this review can be found in the main report.

Key Question 1. For people with nosocomial pneumonia, how does using PK/PD measures to inform decisions about dosing or monitoring antibiotic treatment affect:

- a. clinical response or mechanical ventilation?
- b. morbidity or mortality?
- c. rates of antibiotic-related adverse events?

Key Question 2. For people with nosocomial pneumonia, how does using prolonged or continuous infusions compared with bolus infusions for beta-lactams affect:

- a. clinical response or mechanical ventilation?
- b. morbidity or mortality?
- c. rates of antibiotic-related adverse events?

Key Question 3. Does the evidence for clinical response, mechanical ventilation, morbidity, mortality, or antibiotic-related adverse events differ for subgroups defined by age, sex, race, ethnicity, renal dysfunction or need for dialysis, severity of illness, microorganism, or susceptibility patterns?

Methods

Literature Search Strategy

Search Strategy

We searched MEDLINE®, the Cochrane Library, and the International Pharmaceutical Abstracts for English-language and human-only studies from January 1, 2004 through May 15, 2013. We used either medical subject headings (MeSH) or major headings as search terms when available or key words when appropriate, focusing on terms to describe the relevant population and interventions of interest. We reviewed our search strategy with the technical expert panel (TEP) and incorporated their input into our search strategies. An experienced information scientist (our EPC librarian) ran the searches; another EPC librarian peer-reviewed the searches.

We manually searched reference lists of pertinent reviews and included trials, and background articles on this topic to identify any relevant citations that our searches might have missed. We searched for relevant unpublished studies using ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform.

Inclusion and Exclusion Criteria

We developed eligibility (inclusion and exclusion) criteria with respect to PICOTS and study designs and durations for each KQ. Our review focused on adults (age 18 years and older) who have presumed or confirmed HAP, VAP, or HCAP and are being treated with IV antibiotics. For KQ 1, we required studies to assess an intervention focused on using PK/PD measures to inform decisions: serum concentration, volume of distribution, protein binding, time above MIC, ratio of

AUC to MIC. For KQ 2, we required studies to compare prolonged or continuous infusions with bolus infusions for beta-lactams.

For KQ1 and 3 eligible comparators included: no use of PK/PD measures, different targets of PK/PD measures, or usual care (e.g., physician discretion or judgment, local epidemiology of bacteria and resistance). For KQ2 and 3, eligible comparators were bolus dosing. We required that at least one of our specified outcomes be measured and reported: intermediate outcomes (clinical response, occurrence or duration of mechanical ventilation); health outcomes (mortality, reinfection, relapse, superinfection); and antibiotic adverse events (organ toxicity, hematologic effects, *C. difficile* infection, antibiotic resistance). No limits were placed on timing of the measurement or followup. Nosocomial pneumonia had to have begun in a health care setting (e.g., skilled nursing facility) but was being treated in the hospital (e.g., emergency department, floor, or ICU).

For both intermediate and health outcomes, randomized controlled trials (RCTs), nonrandomized controlled trials, or prospective cohort studies were eligible. For adverse effects data, case-control and retrospective cohort studies were also eligible.

Study Selection

Two trained members of the research team independently reviewed all titles and abstracts for eligibility against our eligibility criteria. Studies marked for possible inclusion by either reviewer underwent a full-text review. Titles and abstracts that lacked adequate information to determine inclusion or exclusion underwent a full-text review.

Two trained members of the research team independently reviewed each full-text article for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agreed that a study did not meet the eligibility criteria, we excluded it. If the reviewers disagreed, they resolved conflicts by discussion and consensus or by consulting a third senior member of the review team.

Data Extraction

For studies meeting inclusion criteria, we extracted important information into evidence tables. For this purpose, we designed and used structured data extraction forms that included characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers extracted relevant data from a second member of the team reviewed all data abstractions for completeness and accuracy.

Risk of Bias Assessment of Individual Studies

To assess the risk of bias (i.e., internal validity) of studies, we applied predefined criteria based on the *AHRQ Methods Guide*.²¹ This approach uses questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias—that is, it addresses issues of adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity.

Two independent reviewers assessed risk of bias for each study, assigning a rating of low, medium, or high risk of bias. Disagreements between the two reviewers were resolved by discussion and consensus or by consulting a third member of the team.

Data Synthesis

We did not find multiple studies for any comparison of interest that reported similar outcomes; for that reason, we could not consider quantitative synthesis (i.e., meta-analysis) of data from included studies. All analyses in this review are, therefore, qualitative. We synthesized data from the included studies in tabular and narrative format. Synthesized evidence was organized by KQ.

Strength of Evidence of the Body of Evidence

We graded the strength of evidence based on the guidance established for the EPC program.²² Developed to grade the overall strength of a body of evidence, this approach incorporates four required domains: risk of bias (including study design and aggregate quality), consistency, directness, and precision of the evidence.

Two reviewers assessed each domain for each key outcome and resolved differences by consensus. The overall grade was based on a qualitative decision taking into account the ratings for the four required domains.

We graded the strength of evidence for the following outcomes: clinical response, mechanical ventilation, treatment failure, mortality, superinfection, and antibiotic related adverse effects.

Applicability

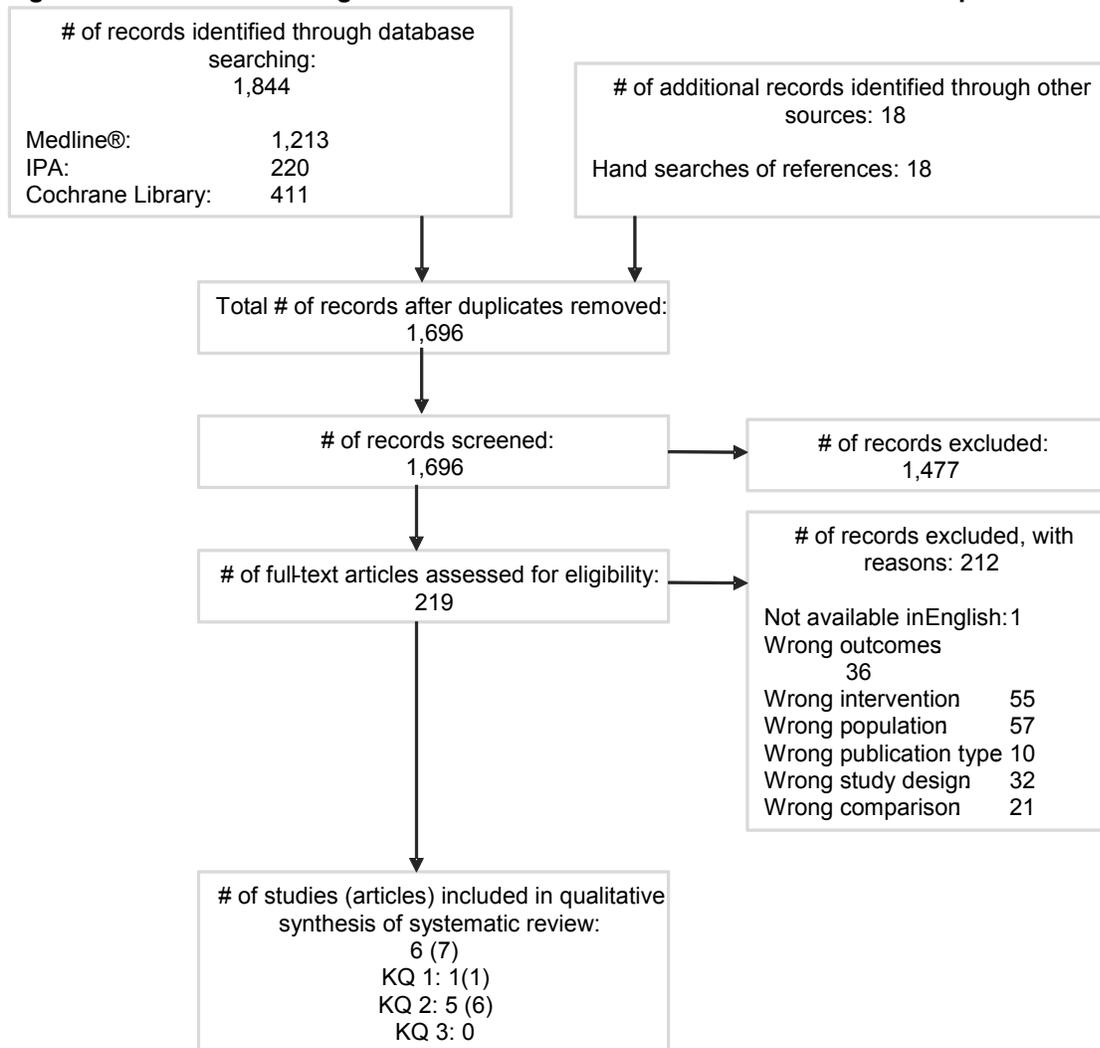
We assessed the applicability of individual studies as well as the applicability of the body of evidence following guidance from the AHRQ *Methods Guide*.²³ For individual studies, we examined factors that may limit applicability based on the PICOTS framework. Some factors identified a priori that could limit the applicability of evidence for this review included the following: severity of illness, whether studies enrolled patients with chronic lung diseases, and settings.

Results

Results of Literature Searches

From an unduplicated pool of 1,696 possible articles, we excluded 1,477 at the title and abstract review stage and another 212 at the full-text review stage (Figure B). We included six studies reported in seven published articles. Of these, one study pertained to KQ 1; five pertained to KQ 2. We identified no studies addressing KQ 3 on subgroups.

Figure B. PRISMA flow diagram for searches for PK/PD uses in nosocomial pneumonia



Four studies were RCTs.²⁴⁻²⁶ One was a prospective cohort study,²⁷ and one was a retrospective cohort study.²⁸ All four RCTs addressed KQ 2. The prospective cohort study pertained to KQ 1; the retrospective cohort study addressed KQ 2. We rated three of the trials as medium risk of bias and one trial and both cohort studies as high risk of bias.

Key Question 1. PK/PD Measures for Dosing or Monitoring

Evidence was insufficient for clinical response, mechanical ventilation, treatment failure, and mortality (Table B). The evidence base was a single prospective cohort study with a high risk of bias. This prospective cohort study was assessed as high risk of bias for multiple reasons, including high risk of measurement bias and confounding. Further, the description of methods were not clearly described. Investigators reported significantly improved outcomes in terms of cure and mortality, however, both measures were problematic.²⁷ It was unclear whether the data reported was based on clinical or microbiologic success data or both, and mortality was combined with “leaving against medical advice.”

Table B. Strength of evidence for using PK/PD measures to influence dosing or monitoring

Outcome	No. of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence
Clinical response	1 prospective cohort (n=638)	High	NA	Indirect	Imprecise	Insufficient
Treatment failure	1 prospective cohort (n=638)	High	NA	Indirect	Imprecise	Insufficient
Mechanical ventilation	1 prospective cohort (n=638)	High	NA	Direct	Imprecise	Insufficient
Mortality (composite of death and leaving AMA)	1 prospective cohort (n=638)	High	NA	Direct	Imprecise	Insufficient

Abbreviations: AMA = against medical advice; n = number; NA = not applicable; PK/PD = pharmacokinetic/pharmacodynamic.

Key Question 2. Prolonged or Continuous Infusions

For KQ 2 (Table C), we graded evidence as insufficient for all outcomes (finding no more than 1 study for any included outcome) and small number of studies with small numbers of patients, generally resulting in unknown consistency and imprecision. Evidence is insufficient to draw conclusions about the effect of continuous infusions compared with the effect of intermittent infusions on outcomes related to clinical response, mechanical ventilation, morbidity, or mortality. The evidence for these outcomes consisted of one small trial.^{25,29} Evidence is also insufficient to draw conclusions about the effect of continuous infusions versus intermittent infusions on the rates of antibiotic-related adverse events.^{24-26,28-30}

Table C. Strength of evidence for comparisons of continuous and intermittent infusion

Outcome Category	Outcome	No. of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence
Intermediate outcomes	Clinical response	1 RCT (n=41)	Medium	NA	Direct	Imprecise	Insufficient
	Mechanical ventilation	1 RCT (n=41)	Medium	NA	Direct	Imprecise	Insufficient
	Treatment failure	1 RCT (n=41)	Medium	NA	Direct	Imprecise	Insufficient
Morbidity and mortality outcomes	Superinfection	1 RCT (n=41)	Medium	NA	Indirect	Imprecise	Insufficient
Antibiotic-related adverse events	Organ toxicity	1 RCT (n=41)	Medium	NA	Indirect	Imprecise	Insufficient
	Hematologic effects	0 (0)	NA	NA	NA	NA	NA
	Clostridium difficile infection	1 RCT (n=41)	Medium	NA	Direct	Imprecise	Insufficient
	Antibiotic resistance	1 RCT (n=41) 1 retrospective cohort (n=83)	Medium	Consistent	Direct Indirect	Imprecise	Insufficient
	Imipenem-related adverse reactions	1 RCT (n=20)	Medium	NA	Unknown	Imprecise	Insufficient
	Adverse events attributed to the dosing regimen of ceftazidime	1 RCT (n=24)	Medium	NA	Unknown	Imprecise	Insufficient
	Infusion-related adverse effects (e.g. phlebitis)	1 RCT (n=34)	Medium	NA	Unknown	Imprecise	Insufficient

Abbreviations: n = number; NA = not applicable (for consistency, all single studies); RCT = randomized controlled trial.

Key Question 3. Subgroup Analyses

We found no studies meeting inclusion criteria. Consequently, evidence was insufficient.

Discussion

Key Findings and Strength of Evidence

Evidence is insufficient to conclude whether using PK/PD measures to inform decisions about dosing or monitoring IV antibiotic treatment (KQ 1) improves intermediate or health outcomes. We only found a single (prospective cohort) study rated as high risk of bias that used PK/PD measures to study the impact of different antibiotic dosing on clinical responses, such as time on mechanical ventilation, treatment failure, and mortality.

Evidence is also insufficient to draw conclusions about the effect of continuous infusions of beta-lactam antibiotics compared with the effect of intermittent infusions on outcomes related to clinical response, mechanical ventilation, morbidity, mortality, or rates of antibiotic-related adverse events (KQ 2). No significant differences were found in clinical response, duration of mechanical ventilation, superinfection, rates of antibiotic-related adverse events or infusion-related adverse effects.

Our review found that very little research has focused on the use of PK/PD measures in dosing or monitoring adult patients with nosocomial pneumonia being treated with IV antibiotics, suggesting that the research has been conducted in *in vitro* and animal studies. In what little is available relating to different PK/PD strategies, investigators have focused largely on mixed populations, including patients with a variety of conditions without reporting outcomes for patients with HAP separately. Other reviews had found limited evidence on patients with HAP.³³ One study compared continuous and intermittent infusion of ceftazidime in critically ill trauma patients with VAP; it found no significant differences in duration of mechanical ventilation.⁴⁵

Emerging microbial resistance concerns motivates clinicians and policymakers alike and have led to renewed efforts to develop more effective strategies for current therapies and the National Institutes of Health has set forth new funding opportunities to encourage new antibiotic developments.

Given the dearth of findings in this review, we cannot propose many ramifications for decisionmaking by either clinicians or policymakers, other than suggesting future research topics. As PK/PD applications for managing nosocomial infections are considered, a few issues arise that warrant consideration from the health care and policy communities.

First, the present PK/PD approaches do not directly consider the variety of antibiotic-resistant genes in pneumonia-causing bacteria; neither, however, do non-PK/PD approaches to managing patients with this disorder. Achieving optimal antibiotic concentrations by PK/PD parameters may not be adequate to eradicate the infection fully or to suppress the possible emergence of resistance in these patients. In such circumstances, PK/PD may actually contribute to the development of resistant organisms and result in treatment failure. These outcomes raise concerns for decisionmakers in various clinical settings (e.g., hospitals and especially ICUs) who need to make decisions about whether and how broadly to use PK/PD strategies in caring for patients with nosocomial pneumonia with IV antibiotics.

Second, the American Thoracic Society (ATS) redefined dosing guidelines based on PK/PD principles and clinical trial efficacy data.¹ Nevertheless, the effectiveness of the dosing strategies

described in these guidelines needs to be validated in the clinical setting in light of increasing microbial resistance, which leads to the relatively short, clinically useful life of most of these antibiotics. These developments concern clinicians and policymakers alike and have led to renewed efforts to develop more effective strategies for using current therapies.

In summary, despite the theoretical advantages of optimizing IV antibiotic dosing using PK/PD principles in patients with nosocomial pneumonia, major gaps in the available evidence preclude our drawing conclusions or examining clinical or policy implications. The near-absence of strong evidence, particularly related to clinical applications, has severely limited the broad adoption of PK/PD dosing optimization in the clinical arena. Below we address the gaps in evidence that might point to additional needed research and to the methods shortcomings in the studies that we were able to use.

Applicability

Based on the guidelines from the AHRQ *Methods Guide*, we found no robust studies addressing the applicability of PK/PD in relation to our PICOTS structure. Studies instead evaluated the measurement of absolute rather than relative benefits and harms, addressed heterogeneous treatment effects, and enrolled heterogeneous patient populations.

Research Gaps

Whether and how using of PK/PD measures to inform dosing decisions for patients with nosocomial pneumonia influences clinical outcomes remains unknown, largely because of the insufficiency of studies per se but also the questionable quality of many of those studies (leading to imprecise findings). As noted, half of the included studies were rated as high risk of bias because of numerous problems with their design or conduct. Moreover, the available studies were sufficiently diverse that they cannot be expected to produce “consistent” findings (and in fact did not).

Key topics not addressed in most investigations are (a) the use of targeted and monitored antibiotic concentrations to tailor antibiotic doses of individual patients and (b) the use of broad applications of PK/PD concepts such as using extended or prolonged infusions of time-dependent antibiotics. Although several studies have reported PK endpoints and findings from Monte Carlo simulated data sets, few in vivo studies have yet been designed to evaluate clinical endpoints. Such endpoints might include the types of intermediate outcomes we sought, such as immediate clinical response or days on a ventilator, but the preferable endpoints would be patient-centered health outcomes (e.g., disease, death). In this review, we had only one RCT that evaluated clinical outcomes in patients with nosocomial pneumonia receiving continuous versus intermittent ceftazidime infusions.²⁹

The effect of optimizing antibiotic dosing based on PK/PD principles for patients with nosocomial pneumonia who fall into various clinical or sociodemographic subgroups is not known. Pharmacokinetic variability based on patient-specific factors such as critical illness, body weight, renal function, or age may influence the magnitude of the effect of PK/PD dose optimization (assuming an effect exists). Furthermore, the infecting pathogen and the MIC of the pathogen are factors that are likely to influence the magnitude of any effect. Certain populations of patients may be more likely to benefit from dose optimizations based on these factors.

Optimizing PK in dosing strategies in the clinical setting may delay the development of antimicrobial resistance. Resistant organisms are a persistent and increasing problem, with methicillin-resistant *S. aureus* infections now accounting for more deaths than AIDS in the

United States. Resistance among Gram-negative organisms is particularly concerning because of the scarcity of new drugs in development with activity against these pathogens. A possible contributor to this emerging resistance is the present approach to dosing antibiotics that is based on the assumptions outlined above for PK/PD. Because present dosing recommendations derive largely from PK/PD studies in healthy volunteers, the recommendations may lead to suboptimal clinical outcomes in patients with HAP (or VAP or HCAP). Furthermore, subtherapeutic concentrations of antibiotics may further contribute to the survival and growth of resistant organisms.

Future investigations could be conducted in large-scale blinded prospective designs intended to compare different PK/PD strategies in patients with HAP. The two goals of these investigations are to better understand the impact of different dosing strategies on meaningful clinical endpoints, such as survival in different patient populations, and on the rate of antibiotic resistance in bacteria.

Conclusions

Despite the theoretical advantages of optimizing IV antibiotic dosing using PK/PD principles in patients with nosocomial pneumonia, major gaps in the available evidence preclude our drawing conclusions or explaining clinical or policy implications.

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Introduction

Background

Nosocomial Pneumonia: Epidemiology

Hospital-acquired (or nosocomial) pneumonia (HAP) is the second most common hospital-acquired infection, occurring especially in the elderly, immunocompromised patients, surgical patients, and individuals receiving enteral feeding through a nasogastric tube. The incidence rates for HAP, which can occur in all areas of hospitals, range from 5 to more than 20 per 1,000 admissions.^{1,2}

HAP is the leading cause of hospital-acquired infection in the intensive care unit (ICU).¹ Almost one-third of HAP episodes are acquired in ICUs;³ as many as 90 percent of ICU cases may be ventilator associated.^{3,4} In the ICU setting, HAP accounts for up to 25 percent of all infections and for more than 50 percent of the antibiotics prescribed.¹

Guidelines issued in 2005 by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) provide the following definitions for HAP, ventilator-associated pneumonia (VAP), and health care-associated pneumonia (HCAP):¹

- HAP is a pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission. Clinicians may manage HAP patients in a hospital ward or in an ICU when the illness is more severe. Some patients may require intubation after developing severe HAP; in these cases, clinicians should manage them in ways similar to treating patients with VAP.
- VAP is a pneumonia that presents more than 48 hours after endotracheal intubation. It is a severe type of HAP because of the difficulty in treating it, and its prognosis is poor.⁵
- HCAP is a pneumonia that develops in any patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic.

Unless specified otherwise, the term “HAP” includes VAP and HCAP. Most of the principles of HAP and VAP overlap with HCAP.

HAP is most often caused by bacterial pathogens, and it may be polymicrobial. Aerobic Gram-negative bacilli, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* species, are the most common causes of HAP. Cases of infections caused by Gram-positive cocci, including *Staphylococcus aureus* (*S. aureus*), are becoming more common in the United States. HAP caused by *S. aureus* is found with greater frequency in patients with diabetes mellitus, patients with head trauma, and patients hospitalized in ICUs. HAP caused by viral or fungal pathogens is rare in immunocompetent patients.¹

HAP is associated with increased morbidity and mortality, longer lengths of inpatient stays, and higher costs of care despite advances in antimicrobial therapy, supportive care, and prevention. For example, episodes of HAP that are not associated with ventilator use raise both hospital lengths of stay and costs of care; in one report from Asian countries, they were associated with death rates of between 27 percent and 50 percent.² Concerns in the United States

and abroad about the increasing rates of superinfection (i.e., infection with a new organism) and multidrug-resistant pathogens call for strategies to optimize existing antibiotic treatment for HAP.^{6,7}

Patients who have received mechanical ventilation are at the greatest risk for nosocomial pneumonia; intubation increases a patient's HAP risk by 6 to 21 times. Mortality from VAP among patients who have acquired VAP in ICUs can be higher for patients who receive inadequate empirical therapy.¹¹ Additional costs per episode of VAP may be as high as \$40,000.¹² Beyond mechanical ventilation, numerous other factors may increase a patient's risk for nosocomial pneumonia:¹⁰

- age >70 years
- chronic lung disease
- depressed consciousness
- aspiration
- chest surgery
- presence of an intracranial pressure monitor or nasogastric tube
- use of acid-suppressing medications
- transport from the ICU for diagnostic or therapeutic procedures
- previous antibiotic exposure, particularly to third-generation cephalosporins
- reintubation or prolonged intubation
- hospitalization during the fall or winter season
- mechanical ventilation for acute respiratory distress syndrome
- frequent ventilator circuit changes
- use of paralytic agents
- presence of various underlying illness

Nosocomial Infection: Treatment

Appropriate antibiotic therapy has been shown to improve survival significantly for patients with HAP.¹³⁻¹⁶ Relevant antibiotics for treating patients with HAP include broad spectrum beta-lactams, vancomycin, and aminoglycosides, among others. Table 1 lists antibiotic classes and individual agents that might be used to treat HAP; bold items are those used most often.

Optimal treatment involves choosing the right drug or combination of drugs, the proper dose and route of administration, the appropriate duration, and is followed by de-escalation to pathogen-directed therapy once culture and susceptibility results are known.¹ Subtherapeutic dosing of antibiotics has been associated with poorer clinical outcomes and emergence of antibiotic resistance.¹⁷⁻²⁰

Optimal dosing of antibiotics based on principles of pharmacokinetics and pharmacodynamics (PK/PD) has the potential to improve outcomes and prevent the development of resistance in patients with HAP. PK is the study of the time course of drug absorption, distribution, metabolism, and excretion. The primary goals of clinical PK include enhancing efficacy and decreasing toxicity of an individual patient's drug therapy. PD refers to the relationship between the concentration of the drug at the site of action and the resulting effect. Antibiotic PD relates PK parameters to the ability of an antibiotic to kill or inhibit growth of bacterial pathogens.²¹ Antibiotics can be classified based on PD characteristics that affect

bacterial killing in relation to the minimum inhibitory concentration (MIC) of the organism (see below).

Table 1. Intravenous antibiotics for which PK/PD measures could be used

Drug Class	Drug^a
Aminoglycosides	Gentamicin Tobramycin Amikacin
Beta-lactams Penicillins	Penicillin G Oxacillin Nafcillin
Beta-lactam/Beta-lactamase inhibitors	Ampicillin/sulbactam Piperacillin/tazobactam Ticarcillin/clavulanic acid
Cephalosporins	Cefazolin Ceftriaxone Cefotaxime Ceftazidime Cefepime Ceftaroline
Monobactams	Aztreonam
Carbapenems	Doripenem Ertapenem Imipenem Meropenem
Fluoroquinolones	Levofloxacin Ciprofloxacin Moxifloxacin
Glycopeptides	Vancomycin
Glycylcyclines	Tigecycline
Oxazolidinone	Linezolid
Polymyxin	Colistin (also called colistimethate sodium)
Rifamycins	Rifampin Rifampicin
Tetracyclines	Doxycycline Minocycline

^a Drug names in bold represent intravenous antibiotics most commonly used to treat nosocomial pneumonia.

To improve the effectiveness of the available antibiotics for nosocomial pneumonia, the 2005 ATS/IDSA guidelines recommended considering PK/PD properties when selecting an antibiotic regimen, dosage, and route of administration. The goal of these guidelines is to provide recommendations for the selection of adequate therapy and thereby achieve optimal patient outcomes. Because this antibiotic dosing logic is based on in vitro and in vivo observations, it may not account for the heterogeneity of patient populations with HAP, the complex pathologic environment in the infected lung, and the drug concentration achieved at the site of the pneumonia. Current antibiotic dosing strategies also do not directly consider the variety of antibiotic resistance mechanisms in bacteria that contribute to the persistence of HAP pneumonia. Suboptimal antibiotic concentrations at the site of infection may not eradicate resistant organisms; may in turn lead to treatment failure, and/ or contribute to emerging antibiotic resistance.

Concerns in the United States and abroad about the increasing rates of superinfection (i.e., infection with a new organism) and new resistance patterns in pathogens call for strategies to optimize existing antibiotic treatment options for HAP.^{6,7} Antibiotic resistance is a growing and significant threat to public health. The incidences of drug resistance among many common HAP

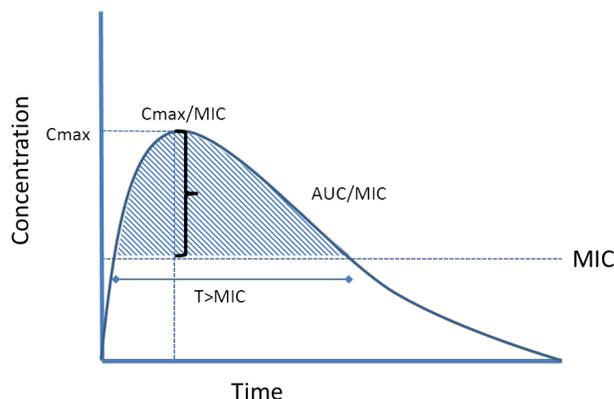
pathogens has increased dramatically over the past three decades. During the same period of time, the number new antibiotics developed has decreased. With fewer antibiotic options, it becomes increasingly important to ensure the appropriate and judicious use of these drugs.^{8,9} While optimization of antibiotic dosing is important to improve individual patient outcomes, optimal antimicrobial exposure may also serve to prevent the emergence of resistant populations of organisms. Subtherapeutic concentrations of antibiotics may contribute to the emergence or acceleration of resistance. Consequently the use of PK and PD measures to guide dosing of antibiotics has important implications, not only for the individual patient being treated, but public health concerns as well.

Use of Pharmacokinetic and Pharmacodynamic Measures for Dosing and Monitoring of Antibiotics

This review aims to document the impact of contemporary approaches to PK/PD-guided dosing of intravenous (IV) antibiotic therapy on clinical outcomes for patients with HAP. In general, antibiotics are grouped into one of three categories based on their mode of bacterial killing: (1) concentration dependent, (2) time dependent, or (3) a combination of concentration and time dependent. These three modes are expressed as ratios to the MIC of the organisms (Figure 1).

- Concentration-dependent antibiotic: Peak concentration to MIC (expressed as C_{\max}/MIC)
- Time-dependent antibiotic: Time that the serum concentration is greater than the MIC (expressed as $T > \text{MIC}$)
- Area under the concentration-time curve (AUC) to MIC (expressed as AUC/MIC).

Figure 1. Ratios related to the minimum inhibitory concentration of the organisms



Abbreviations: AUC = antibiotic area under the curve; AUC/MIC = the ratio of the antibiotic area under the curve to the time above the minimum inhibitory concentration needed to inhibit microorganisms; C_{\max} = the maximum serum concentration needed to inhibit microorganisms; C_{\max}/MIC = ratio of maximum serum concentration (or peak) to the time above the minimum inhibitory concentration needed to inhibit microorganisms; MIC = minimal inhibitory concentration; T = time.

Given the PK/PD properties of antibiotics, clinicians can optimize the PD effects of antibiotics by making decisions about dosing strategies. For example, to optimize the PD effect of a concentration-dependent antibiotic, clinicians may choose to increase the dose, resulting in a higher C_{\max}/MIC ratio.

The traditional method of aminoglycoside dosing has been to divide the total daily dose into two or three equal doses. Based on PD evidence revealing concentration-dependent action, however, many clinicians have adopted the practice of administering aminoglycosides using an

extended-interval dosing scheme; doing so enables them to take advantage of the concentration-dependent effects of the drug. A target of $C_{\max}/MIC > 10$ has been proposed. This target is based on retrospective clinical data, including data in patients with nosocomial pneumonia, correlating clinical response with specific C_{\max}/MIC targets.^{22,23} To achieve this target, the total aminoglycoside daily dose is administered as a single bolus infusion (i.e., a relatively large dose of medication administered into a vein in a short period) over 30 to 60 minutes instead of the traditional divided doses.

For time-dependent antibiotics such as beta-lactams, strategies of prolonged or continuous infusions have been employed to optimize the $T > MIC$ ratio. The standard administration method for IV beta-lactam antibiotics is intermittent bolus dosing. PD data have shown, however, that administration of beta-lactam antibiotics by prolonged infusions produces a higher $T > MIC$ ratio than does intermittent dosing. A target $T > MIC$ of at least 50 to 70 percent of the dosing interval has been proposed based on studies in animal infection models.²⁴⁻²⁷ The use of prolonged or continuous infusions of beta-lactam antibiotics, instead of intermittent bolus dosing, should increase the percentage of time that antibiotic concentrations are above the MIC in the serum; this may correlate with efficacy, especially for organisms with high MICs.

For antibiotics in which the AUC/MIC ratio is the predictor of efficacy, such as vancomycin, clinicians can use concentration monitoring to achieve a specific AUC/MIC target to optimize dosing. Vancomycin monitoring guidelines were published in 2009 by the Society of Infectious Diseases Pharmacists, the American Society of Hospital Pharmacists, and the IDSA.²⁸ These guidelines recommend a target AUC/MIC ratio of 400 for optimal efficacy for vancomycin. Because serum trough concentration monitoring (to determine the minimum concentration of a drug in the serum at the end of a dosing interval) is more practical than AUC monitoring in clinical settings, a goal trough concentration of 15 mg/L to 20 mg/L is recommended for the treatment of HAP caused by methicillin-resistant *S. aureus* with an $MIC \leq 1$ mg/L. For more resistant organisms with an $MIC > 1$ mg/L, the target AUC/MIC of 400 becomes more difficult with standard dosing. The recommendations from this guideline were based on PK analyses and retrospective, observational studies, including one retrospective investigation of patients with pneumonia caused by *S. aureus*.²⁹ The clinical benefit of various vancomycin targets remains a subject of controversy.

PD targets become more difficult to achieve as the MIC for an organism increases and the organism becomes more resistant. As the prevalence of antibiotic-resistant bacteria continues to rise, particularly among critically ill patients, choosing the optimal antibiotic dosing regimen is important to increase the likelihood of clinical success. The optimal dosing regimen will achieve the appropriate PD target without increasing the risk of concentration-related toxicities. For drugs with a narrow therapeutic index (i.e., ones with little difference between toxic and subtherapeutic concentrations), such as vancomycin and the aminoglycosides, the risk of toxicities is often a dose-limiting factor.

The probability of attaining the PD target changes not only with the organism MIC but also with variations in patient-specific factors. The efficacy of an antibiotic depends on its ability to reach the site of infection in sufficient concentrations to inhibit bacterial activity.³⁰ Optimizing PK/PD can increase the likelihood of obtaining adequate concentrations of the appropriate drug and enhancing outcomes for patients with HAP. However, in critically ill patients, alterations in fluid distribution, homeostasis, hemodynamic state, microcirculation, and organ function are common. These factors are essential to understanding and choosing an effective therapeutic regimen, and they can affect both PK and PD properties.^{30,31}

A recent multicenter study demonstrated significant variability in antibiotic trough concentrations in critically ill patients who were receiving continuous renal replacement therapy; the intensity of continuous renal replacement therapy had not predicted such variability.³² This observation suggested that desirable clinical results cannot reliably be achieved with empiric dosing. Current recommended dosing strategies that are based on animal or in vitro models or on data from patients who are not critically ill may not account for these factors; this problem puts critically ill patients at risk of treatment failure, adverse effects from drug toxicity, antibiotic resistance, and death.

In their consensus document on controversial issues for treating critically ill patients with HAP, Franzetti et al. recommended using PK/PD parameters, particularly trough serum concentration monitoring for vancomycin.³³ They based their guidance on evidence that optimizing PK/PD parameters may prevent treatment failure and resistance; it may also reduce nephrotoxicity (severe negative effects on the kidneys) in patients who are receiving aggressive dosing, concurrent nephrotoxic drugs, or prolonged courses of therapy and in patients with unstable renal function.

Scope and Key Questions

Scope of This Review

The main objective of this report is to document and present the findings from a systematic review of the evidence concerning use of PK/PD methods for treating nosocomial pneumonia infections. We are not addressing community-acquired pneumonia or nosocomial pneumonia in children or adolescents.

As presented in more detail in Methods, we focus our analysis on detailed specifications for populations, interventions, comparators, outcomes, timing of measurement or followup, and settings (PICOTS). Briefly, populations include adults who have presumed or confirmed HAP, VAP, or HCAP and who are being treated with IV antibiotic treatment. We look at benefits defined for both intermediate outcomes (clinical response; use of ventilators) and health outcomes (morbidity and mortality); we also examine evidence about adverse events (harms). We examine evidence relating to nosocomial pneumonia that begins in the hospital setting (e.g., emergency department, floor, or ICU) and relating to treatment that continues in other settings; we also include studies of patients who have acquired nosocomial pneumonia in a nursing home setting.

This review is relevant to several dilemmas that clinicians face about how best to select doses and to monitor the use of IV antibiotics for these severely ill patients while taking account of the various PD properties that different IV antibiotics have various patient-specific factors, and resistance patterns of the pathogens. Of concern are both presumed benefits and harms of using PK/PD measures for these purposes. It also attempts to address one very specific question concerning the beta-lactam class of antibiotics. Finally, we examine what may be known about how outcomes (benefits or harms) relate to patient populations characterized by sociodemographic or clinical characteristics.

Key Questions

We address three Key Questions (KQs). Figure 2 presents the analytic framework used to guide this review. The KQs and subquestions are noted in relationship to the direct or indirect linkages depicted in the figure.

Key Question 1. For people with nosocomial pneumonia, how does using PK/PD measures to inform decisions about dosing or monitoring antibiotic treatment affect:

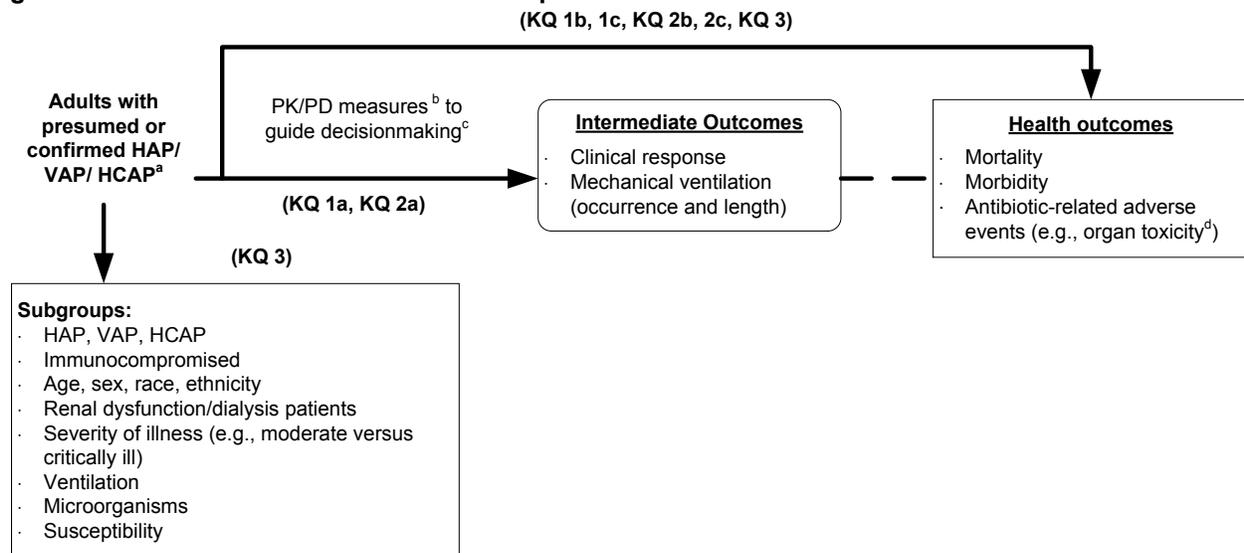
- a. clinical response or mechanical ventilation?
- b. morbidity or mortality?
- c. rates of antibiotic-related adverse events?

Key Question 2. For people with nosocomial pneumonia, how does using prolonged or continuous infusions compared with bolus infusions for beta-lactams affect:

- a. clinical response or mechanical ventilation?
- b. morbidity or mortality?
- c. rates of antibiotic-related adverse events?

Key Question 3. Does the evidence for clinical response, mechanical ventilation, morbidity, mortality, or antibiotic-related adverse events differ for subgroups defined by age, sex, race, ethnicity, renal dysfunction or need for dialysis, severity of illness, microorganism, or susceptibility patterns?

Figure 2. Analytic framework for use of pharmacokinetic/pharmacodynamic (PK/PD) measures to guide antibiotic treatment for nosocomial pneumonia



^a Does not include community-acquired pneumonia but does include nursing-home-acquired pneumonia.

^b Serum concentration, volume of distribution, MIC, ratio of AUC to MIC, protein binding.

^c Dosing or monitoring treatment

^d Toxicity affecting the kidneys, liver, ears, nervous system, and other organs.

Abbreviations: AUC = antibiotic area under the curve; CPIS = Clinical Pulmonary Infection Score; HAP = hospital-acquired pneumonia; HCAP = health care-associated pneumonia; KQ = Key Questions; MIC = minimum inhibitory concentration; PD = pharmacodynamic; PK = pharmacokinetic; VAP = ventilator-associated pneumonia.

Organization of This Report

The remainder of the review describes our methods in detail and presents the results of our synthesis of the literature with summary tables and the strength of evidence grades for major comparisons and outcomes. The discussion section offers our conclusions, summarizes our findings, and provides other information relevant to interpreting this work for clinical practice and future research. References, a list of acronyms and abbreviations, and a glossary of terms follow the Discussion section.

Appendix A contains the exact search strings we used in our literature searches. Appendix B presents the risk of bias assessments of individual studies in this review. Studies excluded at the stage of reviewing full-text articles with reasons for exclusion are presented in Appendix C. Evidence tables appear in Appendix D.

Methods

The methods for this comparative effectiveness review follow the guidance provided in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (www.effectivehealthcare.ahrq.gov/methodsguide.cfm) for the Evidence-based Practice Center (EPC) program. The main sections in this chapter reflect the elements of the protocol established for this review. Certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.³⁴ All methods and analyses were determined a priori.

Topic Refinement and Review Protocol

During the topic development and refinement processes, we engaged in a public process to develop a draft and final protocol for the review. We generated an analytic framework, preliminary Key Questions (KQs), and preliminary inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, timing, settings). Our processes were guided by information provided by the topic nominator; other methods and content experts; and Key Informants (KIs) We also conducted a scan of the relevant literature.

We worked with five KIs during the topic refinement; all five also served as members of our Technical Expert Panel (TEP) for this report. They represented critical care medicine, pulmonology, infectious disease, infectious disease pharmacy, and payers. TEP members participated in conference calls and discussions through e-mail to review the analytic framework, KQs, and PICOTS; discuss the preliminary assessment of the literature; provide input on the information and categories included in evidence tables; and provide input on the data analysis plan.

Our KQs were posted for public comment on AHRQ's Effective Health Care Web site (www.effectivehealthcare.ahrq.gov) from March 22, 2013, through April 18, 2013. We revised them as needed after reviewing the comments and discussing them with the TEP to include dose-monitoring studies, in which no therapeutic drug monitoring occurs during the studies but applies the PK/PD principles. We then drafted a protocol for the review that was posted on the same Web site from July 19, 2013. Its PROSPERO registration number is CRD42013005309.

Literature Search Strategy

Search Strategy

To identify articles relevant to each KQ, we searched MEDLINE®, the Cochrane Library, and the International Pharmaceutical Abstracts from January 1, 2004 through May 15, 2013 (Appendix A presents the full search strategy). We used either medical subject headings (MeSH) or major headings as search terms when available or key words when appropriate, focusing on terms to describe the relevant population and interventions of interest. We reviewed our search strategy with the TEP and incorporated their input into our search strategies. An experienced information scientist (our EPC librarian) ran the searches; another information scientist (EPC librarian) peer-reviewed the searches.

We limited the electronic searches to English-language and human-only studies. We did not limit searches by date. We manually searched reference lists of pertinent reviews and included trials, and background articles on this topic to identify any relevant citations that our searches might have missed. We imported all citations into an EndNote®X4 electronic database.

We searched for unpublished studies relevant to this review using ClinicalTrials.gov and the World Health Organization’s International Clinical Trials Registry Platform. In addition, the AHRQ Scientific Resource Center requested scientific information packets (SIPs) from relevant pharmaceutical and test manufacturing companies, asking for any unpublished studies or data relevant for this comparative effectiveness review (CER). We received no SIPs (as of mid-September 2013).

Inclusion and Exclusion Criteria

We developed eligibility (inclusion and exclusion) criteria with respect to PICOTS and study designs and durations for each KQ (Table 2). We required that at least one of our specified outcomes be measured and reported. For both intermediate outcomes and health outcomes, randomized controlled trials (RCTs), nonrandomized controlled trials, or prospective cohort studies were eligible. For adverse effects data, case-control and retrospective cohort studies were also eligible.

Table 2. Eligibility criteria for review of PK/PD measures for nosocomial pneumonia

Criteria	Inclusion Criteria	Exclusion Criteria
Population	Adults (age 18 years or older) who have presumed or confirmed HAP, VAP, or HCAP and are being treated with intravenous antibiotics (listed in Table 1)	<ul style="list-style-type: none"> • Children and adolescents under 18 years of age • Fungal pneumonia • Other methods of administration (e.g., inhaled antibiotics)
Interventions	<ul style="list-style-type: none"> • KQ 1 and KQ 3: Use of PK/PD measures for dosing and monitoring intravenous antibiotics: <ul style="list-style-type: none"> ○ Serum concentration ○ Volume of distribution ○ Protein binding ○ Time above MIC ○ Ratio of AUC to MIC • KQ 2 and KQ 3: Prolonged or continuous infusion 	<ul style="list-style-type: none"> • No intervention
Comparators	<ul style="list-style-type: none"> • KQ 1 and KQ 3: <ul style="list-style-type: none"> ○ No use of PK/PD measures ○ Different targets of PK/PD measures ○ Usual care (e.g., physician discretion or judgment, local epidemiology of bacteria and resistance) • KQ 2 and KQ 3: Bolus dosing 	<ul style="list-style-type: none"> • No comparator • Studies in which only serum concentration is measured, without targeting different serum concentration levels
Outcomes	<ul style="list-style-type: none"> • KQ 1a, KQ 2a, and KQ 3: Intermediate outcomes <ul style="list-style-type: none"> ○ Clinical response ○ Mechanical ventilation (occurrence or length) • KQ 1b, KQ 2b, and KQ 3: Health outcomes <ul style="list-style-type: none"> • Mortality <ul style="list-style-type: none"> ○ In hospital ○ Within 30 days of discharge ○ All-cause mortality ○ Mortality due to pneumonia 	<ul style="list-style-type: none"> • No outcomes of interest

Table 2. Eligibility criteria for review of PK/PD measures for nosocomial pneumonia (continued)

Criteria	Inclusion Criteria	Exclusion Criteria
Outcomes (continued)	<ul style="list-style-type: none"> • Morbidity <ul style="list-style-type: none"> ○ Reinfection, or two episodes of pneumonia with different pathogens <ul style="list-style-type: none"> ▪ Relapse, or second episode of pneumonia with the same pathogen ▪ Superinfection, or infection with multiple pathogens <p>KQ 1c, KQ 2c, and KQ 3: Antibiotic-related adverse events</p> <ul style="list-style-type: none"> ○ Organ toxicity (e.g., hepatotoxicity, nephrotoxicity) ○ Hematologic effects (e.g., anemia, thrombocytopenia) ○ Clostridium difficile infection ○ Antibiotic resistance (reported at either the patient or the unit level) 	
Timing (length of followup)	No limits	Not applicable
Settings	<ul style="list-style-type: none"> • Treatment beginning in the hospital (emergency department, floor, or ICU) • Treatment continuing in other settings (e.g., in the home or in a skilled nursing facility) 	<ul style="list-style-type: none"> • Treatment beginning in other settings, such as nursing homes
Admissible evidence (study design and other criteria)	<ul style="list-style-type: none"> • Original research; eligible study designs include: • For all KQs: randomized controlled trials with masking of subjects and providers (i.e., double-blind), nonrandomized controlled trials, or prospective cohort studies with an eligible comparison group • For KQ 1c, KQ 2c, and KQ 3 on adverse events: all the above plus case-control studies and retrospective cohorts 	<ul style="list-style-type: none"> • Nonsystematic reviews • Systematic reviews • Editorials • Letters to the editor • Articles rated as having high risk of bias • Case reports • Case series • Studies with historical, rather than concurrent, control groups
Publication language	English	All other languages
Geography	No limits	Not applicable
Time period	No date limit; searches to be updated after the draft report goes out for peer review	Not applicable

Abbreviations: AUC = antibiotic area under the curve; HAP = hospital-acquired pneumonia; HCAP = health care-associated pneumonia; ICU = intensive care unit; KQ = Key Question; MIC = minimum inhibitory concentration; PD = pharmacodynamic; PK = pharmacokinetic; VAP = ventilator-associated pneumonia

We did not include studies of fungal pneumonia in this review, because fungal infections would involve a different set of PICOTS from those found in the literature for bacterial infections. Because the report scope was limited to hospital-acquired pneumonia (HAP), ventilator-acquired pneumonia (VAP), or health-care-acquired pneumonia (HCAP), we also did not include studies of community-acquired pneumonia or other pneumonias in which treatment began in a setting other than the hospital. In addition, because of the report's focus on pneumonia, we did not include studies of shock, sepsis, or other infections that did not provide data for nosocomial pneumonia patients. Finally, we excluded studies in which serum concentration had been measured without comparing different serum concentration targets, because this type of intervention would be considered standard of care and is not a study design that is looking at optimization of PK/PD measures to inform treatment decisions.

Study Selection

Two trained members of the research team independently reviewed all titles and abstracts (identified through searches) for eligibility against our inclusion/exclusion criteria. Studies marked for possible inclusion by either reviewer underwent a full-text review. Titles and abstracts that lacked adequate information to determine inclusion or exclusion underwent a full-text review.

We retrieved the full text of all articles included during the title and abstract review phase. Two trained members of the research team independently reviewed each full-text article for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agreed that a study did not meet the eligibility criteria, we excluded it. If the reviewers disagreed, they resolved conflicts by discussion and consensus or by consulting a third senior member of the review team.

All results in both review stages were tracked in an EndNote® database. We recorded the principal reason that each excluded full-text publication did not satisfy the eligibility criteria (Appendix C).

Data Extraction

For studies that met our inclusion criteria, we extracted important information into evidence tables. We designed and used structured data extraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers extracted the relevant data from each included article into the evidence tables. A second member of the team reviewed all data abstractions for completeness and accuracy. We recorded intention-to-treat results if available. All data abstraction was performed using Microsoft Excel® software.

Risk of Bias Assessment of Individual Studies

To assess the risk of bias (i.e., internal validity) of studies, we applied predefined criteria based on the *AHRQ Methods Guide*.³⁵ This approach uses questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias—that is, it addresses issues of adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity.

Two independent reviewers assessed risk of bias for each study. Disagreements between the two reviewers were resolved by discussion and consensus or by consulting a third member of the team.

Studies are rated as low, medium, or high risk of bias. In general terms, results from a study assessed as having low risk of bias are considered to be valid. A study with medium risk of bias is susceptible to some risk of bias but probably not enough to invalidate its results. A study assessed as high risk of bias has significant risk of bias (e.g., stemming from serious issues in design, conduct, or analysis) that may invalidate its results.

Data Synthesis

We did not find multiple studies for any comparison of interest that reported similar outcomes; for that reason, we could not consider quantitative synthesis (i.e., meta-analysis) of the data from the included studies. All analyses in this review are, therefore, qualitative. We

synthesized data from the included studies in tabular and narrative format. Synthesized evidence was organized by KQ.

Strength of Evidence of the Body of Evidence

We graded the strength of evidence based on the guidance established for the EPC Program.³⁶ Developed to grade the overall strength of a body of evidence, this approach incorporates four required domains: risk of bias (including study design and aggregate quality), consistency, directness, and precision of the evidence. Reviewers can also consider other optional domains that may be relevant for some scenarios; these include dose-response association, plausible confounding that would decrease the observed effect, strength of association (i.e., magnitude of effect), and publication bias.

Table 3 describes the grades of evidence that we assigned. We graded the strength of the body of evidence for major outcomes and comparisons relating to the three KQs stated above. Two reviewers assessed each domain for each key outcome and resolved differences by consensus. For each assessment, one of the two reviewers was always an experienced, senior investigator. The overall grade was based on a qualitative decision taking into account the ratings for the four required domains, and, if relevant, ratings of the other domains.

Table 3. Definition of the grades of overall strength of evidence

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Medium	Medium confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Source: Owens et al., 2010³⁶

We graded the strength of evidence for the outcomes deemed to be of greatest importance to clinicians and other stakeholders. Tables showing our assessments for each domain and the resulting strength of evidence grades for each KQ, organized by intervention-comparison pair and outcome, appear in the results section.

Applicability

We assessed the applicability of individual studies as well as the applicability of the body of evidence following guidance from the AHRQ *Methods Guide*.³⁷ For individual studies, we examined factors that may limit applicability based on the PICOTS framework. Such factors may be associated with heterogeneity of treatment effect or the ability to generalize the effectiveness of an intervention to use in everyday practice. Some factors identified a priori that could limit the applicability of evidence for this review included the following: severity of illness, whether studies enrolled patients with chronic lung diseases, and settings.

Peer Review and Public Commentary

The draft report will be reviewed before peer review and public comment by the Task Order Office (TOO) and an AHRQ associate editor (a senior member of another EPC). The draft

report, as revised if needed, will be sent to invited peer reviewers and simultaneously uploaded to the AHRQ Web site where it will be available for public comment for 28 days.

All reviewer comments (both invited and from the public) will be collated and individually addressed. The EPC responses to all comments will be documented in a disposition of comment document, which will be posted on the Effective Health Care Web site about 3 months after Web publication of the evidence report. The authors of the report have final discretion as to how the report will be revised based on the reviewer comments, with oversight by the TOO and Associate Editor.

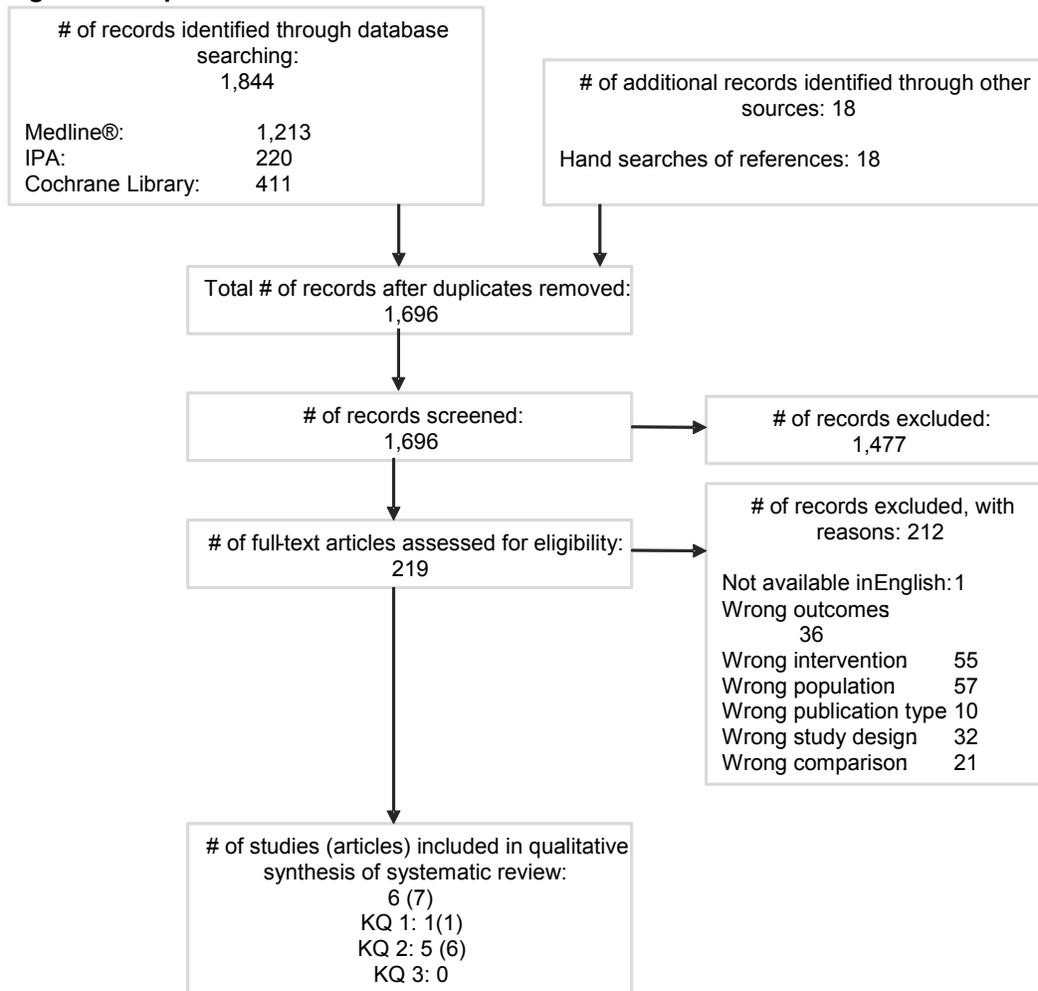
Results

This chapter begins with the results of our literature search and a general description of the included studies. It is then organized by Key Question (KQ) and grouped by intervention (i.e., by drug class or group, whichever is relevant). For each KQ, we give the key points, a more detailed synthesis of the literature, and the strength of evidence (SOE) grades. Additional details for included studies can be found in evidence tables (Appendix D).

Results of Literature Searches

Results of our searches appear in Figure 3. From an unduplicated pool of 1,696 possible articles, we excluded 1,477 at the title and abstract review stage and another 212 at the full-text review stage. We included six studies reported in seven published articles. Of these, one study pertained to KQ 1; five pertained to KQ 2. We identified no studies addressing KQ 3 on subgroups.

Figure 3. Disposition of articles



Description of Included Studies

Four studies were randomized controlled trials (RCTs).³⁸⁻⁴¹ One was a prospective cohort study,⁴² and one was a retrospective cohort study.⁴³ All four RCTs addressed KQ 2; three were conducted by the same group of investigators in the United States, and one was conducted in Germany. The prospective cohort study for KQ 2 was conducted in Italy, and the retrospective cohort study for KQ 1 was performed in Spain. All RCTs were funded by the pharmaceutical industry; the cohort studies were supported by government or an academic institution. We rated three of the trials as medium risk of bias and one trial and both cohort studies as high risk of bias.

Table 4. Characteristics of included studies

Author, Year Design Country Setting	Population N Study Duration Funding	Mean Age (SD) Percentage Female Percentage Nonwhite	Intervention, n Comparator, n	Baseline APACHE II Score, mean (SD)	Risk of Bias
Lorente et al., 2009 ⁴³ Retrospective cohort Spain ICU	Ventilator-acquired pneumonia 83 NR Academic	62.4 (9.8) 21.7% NR	Continuous infusion: 37 Intermittent infusion: 46	Continuous infusion: 16.1 (2.09) Intermittent infusion: 16.2 (2.15)	High
Nicolau et al., 2001 ⁴⁴ McNabb et al., 2001 ⁴⁰ RCT United States ICU	Nosocomial pneumonia 41 (6 non evaluable due to duration of therapy < 5 days) NR Pharmaceutical	51 (18) 34% NR	Continuous infusion: 18 Intermittent infusion: 17	Continuous infusion: 15.5 (6.3) Intermittent infusion: 13.9 (4.4)	Medium
Nicolau et al., 1999 ³⁸ RCT United States ICU	Nosocomial pneumonia 24 NR Pharmaceutical	41.1 (16.4) 37.5% NR	Continuous infusion: 13 Intermittent infusion: 11	Continuous infusion: 14.5 (4.7) Intermittent infusion: 13.8 (5.0)	Medium
Nicolau et al., 1999 ³⁹ RCT United States ICU	Nosocomial pneumonia 34 NR Pharmaceutical	47 (18) 35% NR	Continuous infusion: 17 Intermittent infusion: 17	Continuous infusion: 15 (4) Intermittent infusion: 14 (4)	Medium
Sakka et al., 2007 ⁴¹ RCT Germany ICU	ICU-acquired pneumonia 20 NR Pharmaceutical	60.5 (16) 45% NR	Continuous infusion: 10 Intermittent infusion: 10	Continuous infusion: 26 (6) Intermittent infusion: 28 (5)	High
Scaglione et al., 2009 ⁴² Prospective cohort Italy Hospital	Nosocomial pneumonia 638 NR Government	68.4 (8) NR NR	Serum concentration + MIC: 205 Serum concentration or MIC or no PK/PD measures: 433	Serum concentration + MIC: 17.8 (5.0) Serum concentration or MIC or no PK/PD measures: 19.02 (4.6)	High

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation scale; ICU = intensive care unit; MIC = minimum inhibitory concentration; N = number; NR = not reported; PK/PD = pharmacokinetic/pharmacodynamics; RCT = randomized controlled trial; SD = standard deviation.

Key Question 1. PK/PD Measures for Dosing or Monitoring

Key Points

One prospective cohort study (high risk of bias) found significantly improved outcomes in terms of cure rates and mortality, although both measures were poorly constructed.⁴² Evidence is insufficient to draw conclusions about the effect of using pharmacokinetic/pharmacodynamics (PK/PD) measures for dosing or monitoring on intermediate and health outcomes.

Detailed Synthesis

Scaglione et al. studied a sample of patients receiving mechanical ventilation and who were treated in a special PK/PD program in Italy;⁴² the study excluded immunocompromised patients such as those with HIV, cystic fibrosis, active tuberculosis, lung cancer, or another malignancy metastatic to the lungs, sepsis, or severe renal failure. The authors noted that they did not present their data on the three-way comparison of the impact of measuring and adjusting (versus not measuring and adjusting versus not measuring and not adjusting); however, they concluded that their analyses demonstrated that patients with PK/PD measures and subsequent dose adjustments had the best outcomes. This study was assessed with a high risk of bias because of multiple reasons: unclear methods, outcomes inconsistent with definitions, and potential confounding.

Intermediate and Health Outcomes

The investigators defined clinical success as the absence or improvement of clinically significant symptoms and signs requiring no additional therapy. Those patients who had both PK/PD measures (serum concentration and minimum inhibitory concentration [MIC] monitoring) had a higher percentage classified as a success than those who had only one or no test (82 percent versus 68 percent, p =not reported) (Table 5). Clinical failure was defined as persistence or progression of symptoms and signs, or death. Failure was statistically significantly lower in patients who had both PK/PD measures than in those who did not (18 percent versus 32 percent, $p<0.001$) (Table 5). Patients who received both the serum concentration and MIC monitoring had a nonsignificantly lower duration of mechanical ventilation days than patients who received only one test or none (Table 5). It is important to note that 81 of the 205 patients in the group with both PK/PD measures had antibiotic dose adjustments based on the PK/PD information; however, the authors did not present their analyses based on those who received dose changes or not.

Of those patients who died or left the hospital against medical advice, patients who had both serum concentration and MIC monitoring had significantly lower mortality (10 percent versus 24 percent, $p<0.001$) than those who had one test or none (Table 5). Mortality was, however, a composite measure comprising undefined mortality (did not specify time interval or whether death occurred in the hospital or after discharge) and leaving hospital against medical advice; it is not a validated measure. The authors did not present any other evidence on relapse, reinfection, superinfection, mortality due to pneumonia, mortality in-hospital, or mortality within 30 days of discharge.

Table 5. Clinical response, days of mechanical ventilation, and mortality or other health outcome

Author, Year	Intervention, n Comparator, n	Clinical Success, n (%)	Clinical Failure, n (%)	Duration of Mechanical Ventilation Days, Mean (SD)	Mortality or Leaving Care AMA, n (%)
Scaglione et al., 2009 ⁴²	G1: Serum concentration + MIC: 205 G2: Serum concentration or MIC or no PK/PD measures: 433 (number ventilated: 52)	G1: 168 (82% ^a) G2: 293 (68% ^a) p=NR	G1: 37 (18%) G2: 140 (32%) p<0.001	G1: 4.28 (1.3) G2: 5.39 (1.8) p=0.09	G1: 21 (10) G2: 102 (24) p<0.001

^a calculated by reviewer

Abbreviations: AMA = against medical advice; G = group; MIC = minimum inhibitory concentration; n = number; p = probability; PK/PD = pharmacokinetic/pharmacodynamic; SD = standard deviation.

Antibiotic-Related Adverse Events

This prospective cohort study did not address organ toxicity, hematological effects, *Clostridium difficile* infection, or antibiotic resistance. The investigators state that all treatments were well tolerated and no differences were found between groups.

Strength of Evidence

For KQ 1, evidence was insufficient for the four outcomes addressed: clinical response, mechanical ventilation, treatment failure, and mortality. The evidence base was a single study with a high risk of bias (Table 6).⁴²

Table 6. Strength of evidence for using PK/PD measures to influence dosing or monitoring

Outcome	No. of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence
Clinical response	1 prospective cohort (n=638)	High	NA	Indirect	Imprecise	Insufficient
Treatment failure	1 prospective cohort (n=638)	High	NA	Indirect	Imprecise	Insufficient
Mechanical ventilation	1 prospective cohort (n=638)	High	NA	Direct	Imprecise	Insufficient
Mortality (composite of death and leaving AMA)	1 prospective cohort (n=638)	High	NA	Direct	Imprecise	Insufficient

Abbreviations: AMA = against medical advice; n = number; NA = not applicable; PK/PD = pharmacokinetic/pharmacodynamic.

Key Question 2. Prolonged or Continuous Infusions

Key Points

Evidence is insufficient to draw conclusions about the effect of continuous infusions compared with the effect of intermittent infusions on outcomes related to clinical response, mechanical ventilation, morbidity, or mortality. The evidence consisted of one small trial.^{40,44}

Evidence is insufficient to draw conclusions about the effect of continuous infusions versus intermittent infusions on the rates of antibiotic-related adverse events.^{38-41,43,44}

Detailed Synthesis

KQ 2 addresses the issue of whether using prolonged or continuous infusions as compared with using bolus infusions for beta-lactams affects (a) clinical response or mechanical ventilation, (b) morbidity or mortality, or (c) rates of antibiotic-related adverse events. Our synthesis included five studies (six articles).^{38-41,43,44} All five studies included patients with nosocomial pneumonia in the intensive care unit (ICU) setting. Four were RCTs,^{38-41,44} one was a historical cohort study.⁴³

Of the five studies in our KQ 2 analysis, one trial (n=41) evaluated the effect of continuous versus intermittent administration of beta-lactam antibiotics on intermediate clinical outcomes, duration of mechanical ventilation, and superinfection.^{40,44} This open-label RCT (medium risk of bias) evaluated the clinical efficacy of ceftazidime given as either a continuous or an intermittent infusion to treat patients with nosocomial pneumonia. The investigators excluded immunocompromised patients such as those with AIDS and neutropenia.

Three other RCTs (two medium risk of bias and one high risk of bias) reported rates of antibiotic-related adverse events.^{38,39,41}

We excluded one study (high risk of bias) from the analysis of intermediate outcomes and morbidity or mortality because it was retrospective.⁴³ We included it for the analysis of rates of adverse events.

Intermediate and Health Outcomes

One RCT met our criteria for assessment of intermediate and health outcomes. It reported clinical response, length of mechanical ventilation, and superinfection (Table 7).^{40,44} It defined clinical cure as complete resolution of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on the chest radiograph; improvement was defined as improvement of signs and symptoms of pneumonia with evidence of infection remaining. Failure was defined as persistence or progression of signs and symptoms of pneumonia, development of new pulmonary or extra-pulmonary clinical findings consistent with active infection, progression of radiographic abnormalities, or death from infection.

Clinical cure, improvement, or failure did not differ significantly between the two groups (Table 7).^{40,44} Duration of mechanical ventilation also did not differ significantly between the groups (Table 7). Finally, for rates of superinfection with methicillin-resistant *S. aureus*, the trial reported superinfection in one patient in the continuous infusion group and no patients in the intermittent infusion group (Table 7). No other evidence on relapse, reinfection, or mortality was presented.

Antibiotic-Related Adverse Events

Five studies (three RCTs; one retrospective and one prospective cohort study) reported information on rates of antibiotic-related adverse events (Table 8). Three of these studies reported no adverse events attributed to the treatment regimens.^{38,39,41} One RCT (n=41) reported nephrotoxicity in three patients—two patients in the continuous infusion group and one patient in the intermittent infusion group; all patients had received concomitant IV tobramycin therapy.^{40,44} This trial also reported *Clostridium difficile* infection in three patients—two patients in the intermittent infusion group and one patient in the continuous infusion group.^{40,44} No study reported on hematological adverse effects.

Table 7. Intermediate and health outcomes

Author, Year	Intervention, n Comparator, n	Clinical response	Duration of mechanical ventilation	Superinfection
Nicolau et al., 2001 ⁴⁴	G1: Intermittent Infusion: 18	Cure: G1: 6 (33%)	G1: 8.3 (4.3)	G1: 1 (5.6%)
McNabb et al., 2001 ⁴⁰	G2: Continuous Infusion: 17	G2: 7 (41%)	G2: 7.9 (4.0) p=0.970	G2: 0 (0%) p=NR
		Improvement : G1: 9 (50%) G2: 9 (53%)		
		Failure: G1: 3 (17%) G2: 1 (6%)		
p=0.592 for all three measures				

Abbreviations: G = group; n = number; NR = not reported; p = probability.

Table 8. Antibiotic-related adverse event outcomes

Author, Year	Intervention, n Comparator, n	Outcome	Results, n (%)
Lorente et al., 2009 ⁴³	G1: Continuous infusion: 37 G2: Intermittent infusion: 46	Antibiotic resistance	G1: 0 (0%) G2: 0 (0%) p=NR
Nicolau et al., 2001 ⁴⁴	G1: Continuous Infusion: 18 G2. Intermittent infusion: 17	Antibiotic resistance	G1: 0 (0%) G2: 0 (0%) p=NR
McNabb, 2001 ⁴⁰		<i>Clostridium difficile</i> infection	G1: 1 (5.6%) G2: 2 (11.8%) p=NR
		Nephrotoxicity related to tobramycin	G1: 2 (11.1%) G2: 1 (5.9%) p=NR
Nicolau et al., 1999 ³⁸	G1:Continuous infusion: 13 G2: Intermittent infusion: 11	Adverse events attributed to the dosing regimen of ceftazidime	G1: 0 (0%) G2: 0 (0%) p=NR
Nicolau et al, 1999 ³⁹	G1: Continuous infusion: 17 G2: Intermittent infusion: 17	Infusion-related adverse effects (e.g., phlebitis)	G1: 0 (0%) G2: 0 (0%) p=NR
Sakka et al., 2007 ⁴¹	G1: Continuous infusion: 10 G2: Intermittent infusion: 10	Imipenem-related adverse reactions (e.g., seizures)	G1: 0 (0%) G2: 0 (0%)

Abbreviations: G = group; n = number; NR = not reported; p = probability.

One RCT and one retrospective cohort study reported on rates of resistance or development of resistance during the study periods.^{40,43,44} The trial prospectively evaluated susceptibility data (333 serial MICs) for the identified isolates,^{40,44} but the investigators reported that they did not observe any development of resistance during the study period in either group. The cohort study reported that no antibiotic resistance was observed during the treatment course in either group.⁴³

Strength of Evidence

For KQ 2, we graded SOE as insufficient for clinical response, duration of mechanical ventilation, morbidity or mortality, and rates of antibiotic-related adverse events due to the small number of studies with small numbers of patients, which generally resulted in unknown consistency and imprecision (Table 9). In addition, aggregate risk of bias was medium or high for all outcomes that we found evidence for.

Key Question 3. Subgroup Analyses

We found no studies meeting inclusion criteria that answer any questions about the impact of using PK/PD measures or principles on intermediate or health outcomes or adverse events for subgroups characterized by age, sex, race, ethnicity, renal dysfunction or need for dialysis, severity of illness, type of microorganism, or susceptibility patterns. Consequently, the SOE was insufficient for subgroup issues.

Table 9. Strength of evidence for comparisons of continuous and intermittent infusion

Outcome Category	Outcome	No. of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence
Intermediate outcomes	Clinical response	1 RCT (n=41)	Medium	NA	Direct	Imprecise	Insufficient
	Mechanical ventilation	1 RCT (n=41)	Medium	NA	Direct	Imprecise	Insufficient
	Treatment failure	1 RCT (n=41)	Medium	NA	Direct	Imprecise	Insufficient
Morbidity and mortality outcomes	Superinfection	1 RCT (n=41)	Medium	NA	Indirect	Imprecise	Insufficient
Antibiotic-related adverse events	Organ toxicity	1 RCT (n=41)	Medium	NA	Indirect	Imprecise	Insufficient
	Hematologic effects	0 (0)	NA	NA	NA	NA	NA
	Clostridium difficile infection	1 RCT (n=41)	Medium	NA	Direct	Imprecise	Insufficient
	Antibiotic resistance	1 RCT (n=41) 1 retrospective cohort (n=83)	Medium	Consistent	Direct	Imprecise	Insufficient
			High	Consistent	Indirect	Imprecise	
	Imipenem-related adverse reactions	1 RCT (n=20)	Medium	NA	Unknown	Imprecise	Insufficient
Adverse events attributed to the dosing regimen of ceftazidime	1 RCT (n=24)	Medium	NA	Unknown	Imprecise	Insufficient	
Infusion-related adverse effects (e.g. phlebitis)	1 RCT (n=34)	Medium	NA	Unknown	Imprecise	Insufficient	

Abbreviations: n = number; NA = not applicable (for consistency, all single studies); RCT = randomized controlled trial.

Discussion

This chapter summarizes the key findings and how they relate to published findings and current clinical practices and policies. We then briefly examine the applicability of our findings and their implications for decisionmaking. Limitations of both the review process and the entire evidence base are also examined as a segue into our discussion of research gaps in this field.

Key Findings and Strength of Evidence

There is a dearth of comparative evidence on the use of PK/PD measures in dosing or monitoring or the use of PK/PD strategies in adult patients with nosocomial pneumonia being treated with IV antibiotics.

The strength of evidence is insufficient to conclude whether using measures to inform decisions about dosing or monitoring intravenous antibiotic treatment (KQ 1) improves intermediate or health outcomes. We only found a single prospective cohort study rated as high risk of bias that used PK/PD measures to study the impact of different antibiotic dosing on clinical responses, such as time on mechanical ventilation, treatment failure, and mortality.

Evidence is also insufficient to draw conclusions about the effect of continuous infusions of beta-lactam antibiotics compared with the effect of intermittent infusions on outcomes related to clinical response, mechanical ventilation, morbidity, mortality, or rates of antibiotic-related adverse events (KQ 2). No significant differences were found in clinical response, duration of mechanical ventilation, superinfection, rates of antibiotic-related adverse events, or infusion-related adverse effects.

Findings in Relation to What Is Already Known

Screening titles and abstracts identified by our searches found that very little research has focused on the use of PK/PD measures in dosing or monitoring adult patients with nosocomial pneumonia being treated with IV antibiotics, suggesting that the research has been conducted in *in vitro* and animal studies. For what little is out there relating to different PK/PD strategies, investigators have studied mixed populations, including patients with a variety of conditions (e.g., sepsis, bacteremia, community-acquired pneumonia, nosocomial pneumonia) without reporting outcomes for patients with HAP, or nosocomial pneumonia (including ventilator-associated pneumonia [VAP] and health care-associated pneumonia [HCAP]) separately. Our review focused solely on HAP and explicitly omitted community-acquired pneumonia.

Two previous reviews had found limited evidence on patients with HAP. A 2010 review by Franzetti and colleagues focused narrowly on treatment (primarily vancomycin) for Gram-positive pathogens.³³ Of the seven studies included in their final analysis, only three retrospective cohorts (published between 2004 and 2007) included HAP; of these, two involved the same patient group with HCAP caused by methicillin-resistant *S. aureus*. These studies were limited by a small sample size and retrospective design. Moreover, they were not focused on the use of PK/PD measures for adjusting dosing. Rather, the investigators used set targets and reported on patient outcomes using those targets, not on monitoring the PK/PD measures and adjusting doses to improve outcomes and reduce harms.

One study (2000) compared continuous and intermittent infusion of ceftazidime in critically ill trauma patients with VAP; it found no significant differences in duration of mechanical ventilation.⁴⁵ Recently, Mohed Hafiz and colleagues critically evaluated the methodological shortcomings of clinical studies comparing intermittent dosing and continuous infusion of beta-

lactam antibiotics in critically ill patients. Some of these shortcomings include inconsistent antibiotic doses and endpoints, heterogeneous patient groups, and small sample sizes.⁴⁶

Emerging microbial resistance concerns motivates clinicians and policymakers alike and have led to renewed efforts to develop more effective strategies for current therapies and the National Institutes of Health has set forth new funding opportunities to encourage new antibiotic developments.

Applicability

Based on the guidelines from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide*, we found no robust studies addressing the applicability of PK/PD in relation to our PICOTS (populations, interventions, comparators, outcomes, timing, settings) structure. Studies instead evaluated the measurement of absolute rather than relative benefits and harms, heterogeneous treatment effects, and heterogeneous patient populations.

Implications for Clinical and Policy Decisionmaking

Given the dearth of findings in this review, we offer suggestions for future research on this topic.

First, the present PK/PD approaches do not directly consider the variety of antibiotic-resistance genes in pneumonia-causing bacteria or other clinical settings. Achieving optimal antibiotic concentrations by PK/PD parameters may not be adequate to eradicate the infection fully or to suppress the emergence of resistance. In such circumstances, PK/PD may actually contribute to the development of resistant organisms and result in treatment failure. These outcomes raise concerns for decisionmakers in various clinical settings (e.g., hospitals and especially intensive care units) who make decisions about whether and how broadly to use PK/PD strategies.

Second, the American Thoracic Society (ATS) redefined dosing guidelines based on PK/PD principles and clinical trial efficacy data.¹ Nevertheless, the effectiveness of the dosing strategies described in these guidelines needs to be validated in the clinical setting in light of increasing microbial resistance, which leads to the relatively short, clinically useful life of most of these antibiotics. These developments concern clinicians and policymakers alike and have led to renewed efforts to develop more effective strategies for using current therapies.

In summary, despite the theoretical advantages of optimizing IV antibiotic dosing using PK/PD principles in patients with nosocomial pneumonia, major gaps in the available evidence preclude our drawing conclusions or examining clinical or policy implications. The near-absence of strong evidence, particularly related to clinical applications, has severely limited the broad adoption of PK/PD dosing optimization in the clinical arena. Below we address the gaps in evidence that might point to additional needed research and to the methods shortcomings in the studies we were able to use.

Limitations of the Comparative Effectiveness Review (CER) Process

This review focused on the comparative effectiveness of using PK/PD measures to monitor and adjust dosing of IV antibiotics for nosocomial pneumonia in comparison with no care, usual care, or different targets of PK/PD measures. Because our focus was only nosocomial pneumonia (i.e., HAP, VAP, and HCAP), we omitted any study involving community-acquired pneumonia

or only healthy volunteers. In addition, we addressed use of PK/PD measures only for IV antibiotics; therefore, studies using oral antibiotics or aerosols were excluded.

CER procedures also expect a consideration of the applicability of the evidence to key populations, major outcomes, and the like. As discussed above, the lack of studies precluded completing this requirement in depth.

Limitations of Evidence Base

This review highlights the limitations of the evidence available. Only six studies met criteria for inclusion, and of these, three were ranked as having a high risk of bias. CERs require rating the risk of bias of all included studies, and the application of internationally accepted methods to do this led to ratings of “high” risk of bias for many studies, which we opted to include in the evidence base. (CERs that adopt a “best evidence” approach might have excluded them from the main analyses, but doing so here would have reduced the evidence base to just three or four studies for KQ 2.) CERs also require grading strength of the bodies of evidence. Again, following accepted Evidence-based Practice Center procedures, we had to conclude that evidence was uniformly insufficient to allow any conclusions to be drawn about the two main KQs.

The evidence from these studies was considered insufficient to draw conclusions because of the small numbers of patients, lack of clinical outcome reporting, aggregate risk of bias, unknown consistency for most outcomes (typically with just one small study reporting most outcomes that had any evidence), and overall lack of precision in measurements.

Several studies were excluded from our analysis because of mixed patient populations, lack of an intervention group, or lack of clinical outcome reporting. The limitations of such studies stemmed from several problems. First, although many studies involved patients with nosocomial pneumonia, the overall study population in these investigations tends to be mixed. Typically, analysts do not report findings specifically for patients with nosocomial pneumonia. For example, studies comparing continuous versus intermittent infusions of beta lactams (KQ 2) often do not focus solely on subjects with HAP nor present their analyses in ways that would have permitted us to extract data on outcomes for HAP patients.

Second, other studies that do focus on patients with HAP do not compare different PK/PD strategies. Instead, they compare different antibiotics or they do not address clinical outcomes. Results from these types of studies do not provide comparative evidence addressing our KQs. At best, such studies could provide only hypothesis-generating evidence for the KQs we addressed in this CER.

Third, several methodological inconsistencies used in these studies limited our review. In general, the trials were small and not powered to demonstrate any significant differences between groups.

Moreover, among the studies we included, we rated half as high risk of bias. Only three were considered medium risk of bias, and none was rated low risk of bias. The main problems were primarily high risk of selection bias and researchers not ruling out any impact from a concurrent intervention or unintended exposure.

Research Gaps

In examining the three KQs in terms of PICOTS, we also were tasked with identifying gaps in the evidence base.

First, whether use of PK/PD measures for informing dosing decisions for patients with nosocomial pneumonia influences clinical outcomes remains unknown, largely because of the absence of studies per se but also the questionable quality of many of those studies (leading to imprecise findings). As noted, half of the included studies were rated as high risk of bias because of numerous problems with their design or conduct. Moreover, the available studies were sufficiently diverse that they cannot be expected to produce “consistent” findings (and in fact did not).

Second, key topics not addressed in most investigations are (a) the use of targeted and monitored antibiotic concentrations to tailor antibiotic doses of individual patients and (b) the use of broad applications of PK/PD concepts such as using extended or prolonged infusions of time-dependent antibiotics. Although several studies have reported PK endpoints and findings from Monte Carlo simulated data sets, few in vivo studies have yet been designed to evaluate clinical endpoints. Such endpoints might include the types of intermediate outcomes we sought, such as immediate clinical response or days on a ventilator, but the preferable endpoints would be patient-centered health outcomes (e.g., disease, death). In this review, we had only one RCT that evaluated clinical outcomes in patients with only nosocomial pneumonia receiving continuous versus intermittent ceftazidime infusions.⁴⁴

Third, the effect of optimizing antibiotic dosing based on PK/PD principles for patients with nosocomial pneumonia who fall into various clinical or sociodemographic subgroups is not known. Pharmacokinetic variability based on patient-specific factors such as critical illness, body weight, renal function, or age may influence the magnitude of the effect of PK/PD dose optimization (assuming an effect exists). Furthermore, the infecting pathogen and the MIC of the pathogen are factors that are likely to influence the magnitude of any effect as well. Certain populations of patients may be more likely to benefit from dose optimizations based on these factors.

Finally, another hole in the evidence is whether the optimization of PK in dosing strategies in the clinical setting may delay the development of antimicrobial resistance. Resistant organisms are a persistent and increasing problem, with methicillin-resistant *S. aureus* infections now accounting for more deaths than AIDS in the United States. Resistance among Gram-negative organisms is particularly concerning because of the scarcity of new drugs in development with activity against these pathogens. A possible contributor to this emerging resistance is the present approach to dosing antibiotics that is based on the assumptions outlined above for PK/PD. Because present dosing recommendations are largely based on PK/PD studies in healthy volunteers, the recommendations may lead to suboptimal clinical outcomes in patients with HAP (or VAP or HCAP). Furthermore, subtherapeutic concentrations of antibiotics may further contribute to the survival and growth of resistant organisms.

Future investigations could be conducted in large-scale blinded prospective designs intended to compare different PK/PD strategies in patients with HAP. The two goals of these investigations are to better understand the impact of different dosing strategies on meaningful clinical endpoints, such as survival in different patient populations, and on their effects on the development of antibiotic resistance in bacteria.

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Appendix A. Exact Search Strings

MEDLINE®:

Search	Most Recent Queries	Result
#1	Search (pneumonia[all fields] OR pneumonia[mesh] OR "pneumonia, bacterial"[mesh] OR "lung inflammation"[all fields] OR "pulmonary inflammation"[all fields] OR "pneumonias"[all fields] OR "pneumonitis"[all fields] OR "pneumonitides"[all fields] OR "HCAP"[all fields] OR "healthcare associated pneumonia"[all fields] OR "VAP"[all fields] OR "ventilator associated pneumonia" OR "HAP"[all fields] OR "hospital-acquired pneumonia"[all fields] OR "Pneumonia, Ventilator-Associated"[mesh])	125685
#2	Search "nosocomial"[all fields] OR "hospital acquired"[all fields] OR "healthcare associated"[all fields] OR "ventilator associated"[all fields] OR "cross infection"[mesh] OR "cross infection"[all fields] OR "nursing home"[all fields] OR "nursing homes"[all fields] OR "intermediate care facility"[all fields] OR "intermediate care facilities"[all fields] OR "skilled nursing facility"[all fields] OR "skilled nursing facility"[all fields] OR "nursing home"[MeSH] OR "intermediate care facilities"[MeSH] OR "skilled nursing facilities"[MeSH] OR ((Heteroresistant OR resistant) AND (VISA[all fields] OR "vancomycin intermediate staphylococcus aureus"[all fields])) OR "Staphylococcus aureus"[all fields] OR "Staphylococcus aureus"[mesh] OR Susceptibility[all fields] OR Resistance[all fields] OR "drug resistance"[mesh] OR "drug resistance"[all fields] OR "drug resistance, bacterial"[mesh] OR "Critical care"[mesh] OR "critical care"[all fields] OR "care, critical"[all fields] OR "intensive care"[mesh] OR "Gram-Negative Bacterial Infections"[mesh] OR "Gram-Negative Bacterial Infection"[all fields] OR "Gram-Positive Bacterial Infections"[mesh] OR "Gram-Positive Bacterial Infections"[all fields]	1487227
#3	Search Sepsis[MeSH] OR Sepsis[tw] OR Pyemia[tw] OR Pyemias[tw] OR Pyohemia[tw] OR Pyohemias[tw] OR Pyaemia[tw] OR Pyaemias[tw] OR Septicemia[tw] OR Septicemias[tw] OR "Blood Poisoning" [tw] OR "Blood Poisonings" [tw] OR Severe Sepsis[tw] OR Bacteremia[MeSH] OR Bacteremia[tw] OR Bacteremias[tw] OR Endotoxemia[MeSH] OR Endotoxemia[tw] OR Endotoxemias[tw] OR "Hemorrhagic Septicemia"[MeSH] OR "Hemorrhagic Septicemia"[tw] OR "Haemorrhagic Septicaemia"[tw] OR "Hemorrhagic Septicaemia"[tw] OR "Haemorrhagic Septicemia"[tw] OR "Hemorrhagic Bacteremia"[tw] OR "Haemorrhagic Bacteremia"[tw] OR "Shock, Septic"[MeSH] OR "Septic Shock"[tw] OR "Toxic Shock"[tw] OR "Toxic Shock Syndrome"[tw] OR "Toxic Shock Syndromes"[tw] OR "Endotoxic Shock"[tw]	141016
#4	Search (#1 AND (#2 OR #3))	45371
#5	Search (pharmacokinetic*[all fields] OR "pharmacokinetics"[mesh] OR "pharmacokinetics"[sh] OR "Area Under Curves"[all fields] OR "Curve, Area Under"[all fields] OR "Curves, Area Under"[all fields] OR "Under Curve, Area"[all fields] OR "Under Curves, Area"[all fields] OR AUC[all fields] OR "Biological Availability"[mesh] OR "biological availability"[all fields] OR "bioavailability"[all fields] OR "Metabolic Clearance Rate"[mesh] OR "metabolic clearance rate"[all fields] OR "Therapeutic Equivalency"[mesh] OR "therapeutic equivalency"[all fields] OR "bioequivalence"[all fields] OR "Tissue Distribution"[mesh] OR "tissue distribution"[all fields] OR "adme"[all fields] OR "admet"[all fields] OR "Absorption/drug effects"[mesh] OR "metabolism/drug effects"[all fields] OR "metabolism"[sh] OR "creatinine clearance"[all fields] OR "metabolic clearance rate"[mesh] OR "volume of	5605147

Search	Most Recent Queries	Result
	distribution"[all fields] OR "apparent volume of distribution"[all fields] OR "rate of infusion"[all fields] OR "dosing rate"[all fields] OR "body fluid compartments"[mesh] OR "onset of action"[all fields] OR "biological half-life"[all fields] OR "Protein binding"[mesh] OR "protein binding"[all fields] OR "Plasma Protein Binding"[all fields] OR "therapeutic index"[all fields] OR "therapeutic ratio"[all fields] OR "Trough level"[all fields] OR "peak level"[all fields] OR "therapeutic drug monitoring"[all fields] OR "drug monitoring"[MeSH])	
#6	Search (pharmacodynamic*[all fields] OR "dose-response relationship, drug"[mesh] OR "drug dose-response relationship"[all fields] OR "dose response relationship, drug"[all fields] OR "antimicrobial pharmacodynamics"[all fields] OR "MIC"[all fields] OR "minimum inhibitory concentration"[all fields] OR "AUC"[all fields] OR "AUCI"[all fields] OR "area under the curve"[all fields] OR "area under the inhibitory curve" OR "microbial sensitivity tests"[mesh] OR "time kill curve"[all fields] OR "time kill"[all fields] OR "time killing curves"[all fields] OR "time killing"[all fields])	475113
#7	Search (Vancomycin[mesh] OR vancomycin[all fields] OR Carbapenems[all fields] OR Thienamycins[all fields] OR Cephalosporins[all fields] OR Cefamandole[all fields] OR Cefazolin[all fields] OR Cefonicid[all fields] OR Cefsulodin[all fields] OR Cephacetrile[all fields] OR Cephalexin[all fields] OR Cephaloridine[all fields] OR Cephamycins[all fields] OR "Clavulanic Acids"[all fields] OR "Clavulanic Acid"[all fields] OR Monobactams[all fields] OR Aztreonam[all fields] OR Moxalactam[all fields] OR Penicillin[all fields] OR penicillins[all fields] OR Amdinocillin[all fields] OR Cyclacillin[all fields] OR Methicillin[all fields] OR Nafcillin[all fields] OR Oxacillin[all fields] OR "Penicillanic Acid"[all fields] OR "Penicillin G"[all fields] OR "Penicillin V"[all fields] OR Sulbactam[all fields] OR Ticarcillin[all fields] OR Aminoglycosides[all fields] OR Anthracyclines[all fields] OR Aclarubicin[all fields] OR Daunorubicin[all fields] OR Plicamycin[all fields] OR "Butirosin Sulfate"[all fields] OR Gentamicins[all fields] OR Sisomicin[all fields] OR "Hygromycin B"[all fields] OR Kanamycin[all fields] OR Amikacin[all fields] OR Dibekacin[all fields] OR Nebramycin[all fields] OR Metrizamide[all fields] OR Neomycin[all fields] OR Framycetin[all fields] OR Paromomycin[all fields] OR Ribostamycin[all fields] OR Puromycin[all fields] OR "Puromycin Aminonucleoside"[all fields] OR Spectinomycin[all fields] OR Streptomycin[all fields] OR "Dihydrostreptomycin Sulfate"[all fields] OR Streptothricins[all fields] OR Streptozocin[all fields] OR Fluoroquinolones[all fields] OR Ciprofloxacin[all fields] OR Fleroxacin[all fields] OR Enoxacin[all fields] OR Norfloxacin[all fields] OR Ofloxacin[all fields] OR Pefloxacin[all fields] OR Ampicillin[MeSH] OR ampicillin[all fields] OR Piperacillin[MeSH] OR piperacillin[all fields] OR Tazobactam[Supplementary Concept] OR tazobactam[all fields] OR Ceftriaxone[MeSH] OR Ceftriaxone[all fields] OR Cefotaxime[MeSH] OR cefotaxime[all fields] OR Ceftazidime[MeSH] OR Ceftazidime[all fields] OR Cefepime[Supplementary Concept] OR cefepime[all fields] OR Ceftaroline[all fields] OR "T 91825"[Supplementary Concept] OR Doripenem[Supplementary Concept] OR doripenem[all fields] OR Ertapenem[Supplementary Concept] OR ertapenem[all fields] OR Imipenem[MeSH] OR imipenem[all fields] OR Meropenem[Supplementary Concept] OR meropenem[all fields] OR ofloxacin[MeSH] OR Levofloxacin[all fields] OR Moxifloxacin[Supplementary Concept] OR moxifloxacin[all fields] OR Tobramycin[MeSH] OR tobramycin[all fields] OR Linezolid[Supplementary Concept] OR linezolid[all fields] OR Colistin[MeSH] OR colistin[all fields] OR colistimethate[Supplementary Concept] OR	370705

Search	Most Recent Queries	Result
	"colistimethate sodium"[all fields] OR rifamycins[MeSH] OR rifampin[MeSH] OR rifampin[all fields] OR rifampicin[all fields] OR tetracyclines[MeSH] OR doxycycline[MeSH] OR doxycycline[all fields] OR minocycline[MeSH] OR minocycline[all fields] OR tigecycline[supplementary concept] OR tigecycline[all fields])	
#8	Search ("anti-bacterial agent"[all fields] OR "anti-bacterial agents"[all fields] OR "antibacterial agent"[all fields] OR "antibacterial agents"[all fields] OR antibiotic*[all fields] OR "Anti-Bacterial Agents"[mesh])	621086
#9	Search ("Editorial"[publication type] OR "Letter"[publication type] OR "Addresses"[publication type] OR "Autobiography"[publication type] OR "Bibliography"[publication type] OR "Biography"[publication type] OR "comment"[publication type] OR "Congresses"[publication type] OR "Consensus Development Conference, NIH"[publication type] OR "Dictionary"[publication type] OR "Directory"[publication type] OR "Festschrift"[publication type] OR "Interactive Tutorial"[publication type] OR "Interview"[publication type] OR "Lectures"[publication type] OR "Legal Cases"[publication type] OR "Legislation"[publication type] OR "Patient Education Handout"[publication type] OR "Periodical Index"[publication type] OR "Portraits"[publication type] OR "Scientific Integrity Review"[publication type] OR "Video-Audio Media"[publication type] OR "Webcasts"[publication type])	1527036
#10	Search (("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields])	107278
#11	Search (#4 AND (#5 OR #6) AND (#7 OR #8))	4233
#12	Search (#11 NOT (#9 OR #10))	4048
#13	Search (#11 NOT (#9 OR #10)) Filters: Humans	3356
#14	Search (#11 NOT (#9 OR #10)) Filters: Other Animals	850
#15	Search (#14 NOT #13)	547
#16	Search (#12 NOT #15)	3501
#17	Search (#16) Filters: English	2636
#18	Search (#16) Filters: English; Adult: 19+ years	1213

Cochrane:

ID	Search	Hits
#1	MeSH descriptor: [Pneumonia] explode all trees	2406
#2	MeSH descriptor: [Pneumonia, Bacterial] explode all trees	643
#3	MeSH descriptor: [Pneumonia, Ventilator-Associated] explode all trees	159
#4	'pneumonia' or 'pneumonia bacterial' or 'lung inflammation' or 'pulmonary inflammation' or 'pneumonias' or 'pneumonitis' or 'pneumonitides'	7518
#5	#1 or #2 or #3 or #4	7588
#6	MeSH descriptor: [Nursing Homes] explode all trees	882
#7	MeSH descriptor: [Skilled Nursing Facilities] explode all trees	51
#8	MeSH descriptor: [Intermediate Care Facilities] explode all trees	13
#9	MeSH descriptor: [Drug Resistance, Bacterial] explode all trees	739

ID	Search	Hits
#10	MeSH descriptor: [Critical Care] explode all trees	1668
#11	MeSH descriptor: [Intensive Care] explode all trees	1029
#12	MeSH descriptor: [Gram-Positive Bacterial Infections] explode all trees	4508
#13	MeSH descriptor: [Gram-Negative Bacterial Infections] explode all trees	5475
#14	'hcap' or 'healthcare associated pneumonia' or 'vap' or 'ventilator associated pneumonia' or 'hap' or 'hospital-acquired pneumonia' or 'pneumonia ventilator-associated' or 'nosocomial' or 'hospital acquired' or 'healthcare associated' or 'ventilator associated' or 'cross infection' or 'nursing home' or 'nursing homes' or 'intermediate care facility' or 'intermediate care facilities' or 'skilled nursing facility' or 'skilled nursing facilities' or heteroresistant or resistant or visa or 'vancomycin intermediate staphylococcus aureus' or 'staphylococcus aureus' or susceptibility or resistance or 'drug resistance' or 'drug resistance bacterial' or 'critical care' or 'care critical' or 'intensive care' or 'gram-negative bacterial infections' or 'gram-negative bacterial infection' or 'gram-positive bacterial infections'	72654
#15	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	79030
#16	MeSH descriptor: [Sepsis] explode all trees	2788
#17	MeSH descriptor: [Bacteremia] explode all trees	687
#18	MeSH descriptor: [Endotoxemia] explode all trees	122
#19	MeSH descriptor: [Hemorrhagic Septicemia] explode all trees	0
#20	MeSH descriptor: [Shock, Septic] explode all trees	382
#21	Sepsis or Pyemia* or Pyohemia* or Pyaemia* or Septicemia* or 'Blood Poisoning' or 'Blood Poisonings' or Bacteremia* or Endotoxemia* or 'Hemorrhagic Septicemia' or 'Haemorrhagic Septicaemia' or 'Hemorrhagic Septicaemia' or 'Haemorrhagic Septicemia' or 'Hemorrhagic Bacteremia' or 'Haemorrhagic Bacteremia' or 'Septic Shock' or 'Toxic Shock' or 'Endotoxic Shock' or 'Severe Sepsis'	6717
#22	#16 or #17 or #18 or #19 or #20 or #21	7257
#23	#5 and (#15 or #22)	4159
#24	MeSH descriptor: [Pharmacokinetics] explode all trees	9715
#25	MeSH descriptor: [Drug Monitoring] explode all trees	933
#26	pharmacokinetic* or 'pharmacokinetics' or 'pharmacokinetic' or 'area under curves' or 'area under curve' or 'curve, area under' or 'curves, area under' or 'under curve, area' or 'under curves, area' or 'auc' or 'biological availability' or 'bioavailability' or 'therapeutic equivalency' or 'bioequivalence' or 'tissue distribution' or 'adme' or 'admet' or 'absorption' or 'metabolism' or 'creatinine clearance' or 'metabolic clearance rate' or 'volume of distribution' or 'apparent volume of distribution' or 'rate of infusion' or 'dosing rate' or 'body fluid compartments' or 'onset of action' or 'biological half-life' or 'protein binding' or 'plasma protein binding' or 'therapeutic index' or 'therapeutic ratio' or 'trough level' or 'peak level'	170788
#27	#24 or #25 or #26	171127
#28	MeSH descriptor: [Dose-Response Relationship, Drug] explode all trees	23091
#29	pharmacodynamic* or 'dose-response relationship, drug' or 'drug dose-response relationship' or 'antimicrobial pharmacodynamics' or 'mic' or 'minimum inhibitory concentration' or 'auc' or 'auic' or 'area under the curve' or 'area under the inhibitory curve' or 'microbial sensitivity tests' or 'microbial sensitivity test' or 'time kill curve' or 'time kill' or 'time killing curves' or 'time killing'	43464
#30	#28 or #29	43464
#31	'vancomycin' or 'carbapenems' or 'thienamycins' or 'cephalosporins' or	20530

ID	Search	Hits
	'cefamandole' or 'cefazolin' or 'cefonicid' or 'cefsulodin' or 'cephacetrile' or 'cephalexin' or 'cephaloridine' or 'cephamycins' or 'clavulanic acids' or 'clavulanic acid' or 'monobactams' or 'aztreonam' or 'moxalactam' or 'penicillin' or 'penicillins' or 'amdinocillin' or 'cyclacillin' or 'methicillin' or 'nafcillin' or 'oxacillin' or 'penicillanic acid' or 'penicillin g' or 'penicillin v' or 'sulbactam' or 'ticarcillin' or 'aminoglycosides' or 'anthracyclines' or 'acliarubicin' or 'daunorubicin' or 'plicamycin' or 'butirosin sulfate' or 'gentamicins' or 'sisomicin' or 'hygromycin b' or 'kanamycin' or 'amikacin' or 'dibekacin' or 'nebramycin' or 'metrizamide' or 'neomycin' or 'framycetin' or 'paromomycin' or 'ribostamycin' or 'puromycin' or 'puromycin aminonucleoside' or 'spectinomycin' or 'streptomycin' or 'dihydrostreptomycin sulfate' or 'streptothricins' or 'streptozocin' or 'fluoroquinolones' or 'ciprofloxacin' or 'fleroxacin' or 'enoxacin' or 'norfloxacin' or 'ofloxacin' or 'pefloxacin' or 'ampicillin' or 'piperacillin' or 'tazobactam' or 'ceftriaxone' or 'cefotaxime' or 'ceftazidime' or 'cefepime' or 'ceftaroline' or 't 91825' or 'doripenem' or 'ertapenem' or 'imipenem' or 'meropenem' or ofloxacin or 'levofloxacin' or 'moxifloxacin' or 'tobramycin' or 'linezolid' or 'colistin' or 'colistimethate' or 'colistimethate sodium' or 'rifamycins' or 'rifampin' or 'rifampicin' or 'tetracyclines' or 'doxycycline' or 'minocycline' or 'tigecycline'	
#32	MeSH descriptor: [Anti-Bacterial Agents] explode all trees	8388
#33	'anti-bacterial agent' or 'anti-bacterial agents' or 'antibacterial agent' or 'antibacterial agents' or antibiotic*	19974
#34	#31 or #32 or #33	31453
#35	#23 and (#27 or #30) and #34	1080
#36	#23 and (#27 or #30) and #34 Limit: Trials	411

IPA:

#	Query	Results
S1	SU Pneumonia	2,205
S2	SU Bacterial Pneumonia	18
S3	SU Ventilator-Associated Pneumonia	2
S4	TX "pneumonia" OR "pneumonia bacterial" OR "lung inflammation" OR "pulmonary inflammation" OR "pneumonias" OR "pneumonitis" OR "pneumonitides"	3,859
S5	S1 OR S2 OR S3 OR S4	3,859
S6	SU Nursing Homes	914
S7	SU Skilled Nursing Facilities	124
S8	SU Intermediate Care Facilities	17
S9	SU Drug Resistance	235
S10	SU Critical Care	2,009
S11	SU Intensive Care Unit	1,748
S12	SU Gram-Positive Bacterial Infections	206
S13	SU Gram-Negative Bacterial Infections	147
S14	TX "hcap" OR "healthcare associated pneumonia" OR "vap" OR "ventilator associated pneumonia" OR "hap" OR "hospital-acquired pneumonia" OR "pneumonia ventilator-associated" OR "nosocomial" OR "hospital acquired"	28,294

#	Query	Results
	OR "healthcare associated" OR "ventilator associated" OR "cross infection" OR "nursing home" OR "nursing homes" OR "intermediate care facility" OR "intermediate care facilities" OR "skilled nursing facility" OR "skilled nursing facilities" OR heteroresistant OR resistant OR visa OR "vancomycin intermediate staphylococcus aureus" OR "staphylococcus aureus" OR susceptibility OR resistance OR "drug resistance" OR "drug resistance bacterial" OR "critical care" OR "care critical" OR "intensive care" OR "gram-negative bacterial infections" OR "gram-negative bacterial infection" OR "gram-positive bacterial infections"	
S15	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14	28,339
S16	SU Sepsis	792
S17	SU Bacteremia	306
S18	SU Endotoxemia	33
S19	SU Hemorrhagic Shock	7
S20	SU Septic Shock	98
S21	TX Sepsis OR Pyemia* OR Pyohemia* OR Pyaemia* OR Septicemia* OR "Blood Poisoning" OR "Blood Poisonings" OR Bacteremia* OR Endotoxemia* OR "Hemorrhagic Septicemia" OR "Haemorrhagic Septicaemia" OR "Hemorrhagic Septicaemia" OR "Haemorrhagic Septicemia" OR "Hemorrhagic Bacteremia" OR "Haemorrhagic Bacteremia" OR "Septic Shock" OR "Toxic Shock" OR "Endotoxic Shock" OR "Severe Sepsis"	3,178
S22	S16 OR S17 OR S18 OR S19 OR S20 OR S21	3,185
S23	S5 AND (S15 OR S22)	1,385
S24	SU Pharmacokinetics	44,211
S25	SU Drug Monitoring	1,009
S26	TX pharmacokinetic* OR "pharmacokinetics" OR "pharmacokinetic" OR "area under curves" OR "area under curve" OR "curve, area under" OR "curves, area under" OR "under curve, area" OR "under curves, area" OR "auc" OR "biological availability" OR "bioavailability" OR "therapeutic equivalency" OR "bioequivalence" OR "tissue distribution" OR "adme" OR "admet" OR "absorption" OR "metabolism" OR "creatinine clearance" OR "metabolic clearance rate" OR "volume of distribution" OR "apparent volume of distribution" OR "rate of infusion" OR "dosing rate" OR "body fluid compartments" OR "onset of action" OR "biological half-life" OR "protein binding" OR "plasma protein binding" OR "therapeutic index" OR "therapeutic ratio" OR "trough level" OR "peak level"	92,393
S27	S24 OR S25 OR S26	93,144
S28	SU Dose-Response Relationship	9
S29	pharmacodynamic* OR "dose-response relationship, drug" OR "drug dose- response relationship" OR "antimicrobial pharmacodynamics" OR "mic" OR "minimum inhibitory concentration" OR "auc" OR "auic" OR "area under the curve" OR "area under the inhibitory curve" OR "microbial sensitivity tests" OR "microbial sensitivity test" OR "time kill curve" OR "time kill" OR "time killing curves" OR "time killing"	21,472
S30	S28 OR S29	21,481
S31	TX "vancomycin" OR "carbapenems" OR "thienamycins" OR "cephalosporins" OR "cefamandole" OR "cefazolin" OR "cefonicid" OR "cefsulodin" OR "cephacetriole" OR "cephalexin" OR "cephaloridine" OR "cephamycins" OR "clavulanic acids" OR "clavulanic acid" OR "monobactams" OR "aztreonam" OR "moxalactam" OR "penicillin" OR "penicillins" OR "amdinocillin" OR "cyclacillin" OR "methicillin" OR "nafcillin"	26,345

#	Query	Results
	OR "oxacillin" OR "penicillanic acid" OR "penicillin g" OR "penicillin v" OR "sulbactam" OR "ticarcillin" OR "aminoglycosides" OR "anthracyclines" OR "aclerubicin" OR "daunorubicin" OR "plicamycin" OR "butirosin sulfate" OR "gentamicins" OR "sisomicin" OR "hygromycin b" OR "kanamycin" OR "amikacin" OR "dibekacin" OR "nebramycin" OR "metrizamide" OR "neomycin" OR "framycetin" OR "paromomycin" OR "ribostamycin" OR "puromycin" OR "puromycin aminonucleoside" OR "spectinomycin" OR "streptomycin" OR "dihydrostreptomycin sulfate" OR "streptothricins" OR "streptozocin" OR "fluoroquinolones" OR "ciprofloxacin" OR "floxacin" OR "enoxacin" OR "norfloxacin" OR "ofloxacin" OR "pefloxacin" OR "ampicillin" OR "piperacillin" OR "tazobactam" OR "ceftriaxone" OR "cefotaxime" OR "ceftazidime" OR "cefepime" OR "ceftaroline" OR "t 91825" OR "doripenem" OR "ertapenem" OR "imipenem" OR "meropenem" OR ofloxacin OR "levofloxacin" OR "moxifloxacin" OR "tobramycin" OR "linezolid" OR "colistin" OR "colistimethate" OR "colistimethate sodium" OR "rifamycins" OR "rifampin" OR "rifampicin" OR "tetracyclines" OR "doxycycline" OR "minocycline" OR "tigecycline"	
S32	SU Anti-Bacterial Agents	19,600
S33	TX "anti-bacterial agent" OR "anti-bacterial agents" OR "antibacterial agent" OR "antibacterial agents" OR antibiotic*	26,571
S34	S31 OR S32 OR S33	41,069
S35	S23 and (S27 OR S30) and S34	220

Total references identified by the main searches = 1844

Total references from main and hand searches, minus duplicates = 1696

Appendix B: Risk of Bias Assessment

In general terms, a “low” risk of bias study has the least risk of bias and its results are considered to be valid. A “medium” risk of bias study is susceptible to some bias but probably not sufficient to invalidate its results. A “high” risk of bias study has significant risk of bias (e.g., stemming from serious errors in design, conduct, or analysis) that may invalidate its results. Two independent reviewers assigned risk of bias ratings for each study. For each article, one of the two reviewers was always an experienced investigator. Disagreements between the two reviewers were resolved by discussion and consensus or by consulting a third member of the team. We gave high risk of bias ratings to studies that had a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories. The most common methodologic shortcomings contributing to high risk of bias ratings were high rates of attrition or differential attrition, inadequate methods used to handle missing data, and lack of intention-to-treat analysis. Below we list the 15 questions used to assess risk of bias for randomized controlled trials and the 10 questions used to assess risk of bias for observational studies. Then, Tables B-1 and B-2 provides the answers to these questions for each study.

Randomized Controlled Trials

Criteria

Was randomization adequate?

Was allocation concealment adequate?

Did strategy for recruiting participants into study differ across study groups?

Were groups similar at baseline?

Were outcome assessors masked?

Were care providers masked?

Were patients masked?

Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?

Did variation from the study protocol compromise the conclusions of the study?

Was overall attrition 20% or higher or was differential attrition 15% or higher?

Did attrition result in a difference in group characteristics between baseline (or randomization) and follow-up?

Did the study use intention-to-treat analysis?

Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?

Were outcome measures equal, valid, and reliable?

Were potential outcomes pre-specified by researchers and were all pre-specified outcomes reported?

Table B-1. Risk of bias ratings for randomized controlled trials, part 1

Author, Year Trial Name	Method of randomization adequate?	Allocation of treatment adequately concealed?	Did strategy for recruiting participants into study differ across study groups?	Baseline characteristics similar between groups? If not, did analysis control for differences?	Were the outcome assessors blinded to the intervention or exposure status of participants?	Were the care providers blinded to the intervention or exposure status of participants?	Were the patients blinded to their intervention or exposure status?
Nicolau, 1999 ¹	Unclear or NR	No	No	Yes	No	Single blinded (unclear who was blinded and who was not)	Unclear who was blinded and who was not
Nicolau, 1999 ²	Unclear or NR	No	No	Yes	No	No mention of blinding	No mention of blinding
Nicolau, 2001 ³ McNabb, 2001 ⁴	Unclear or NR	No	No	Yes	No	Not blinded (open label)	Not blinded (open label)
Sakka, 2007 ⁵	Yes	Unclear or NR	Unclear or NR	Yes	Unclear or NR	Not blinded	Not blinded

Table B-1. Risk of bias ratings for randomized controlled trials, part 2

Author, Year Trial Name	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	Did variation from the study protocol compromise the conclusions of the study?	Was there a high rate of differential or overall attrition? (i.e., $\geq 20\%$ for overall attrition or $\geq 15\%$ for differential attrition)	Did attrition result in a difference in group characteristics between baseline (or randomization) and follow-up?	Is the analysis conducted on an intention-to-treat (ITT) basis?	Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?
Nicolau, 1999 ¹	Unclear or NR	No	No	Yes	No	Yes
Nicolau, 1999 ²	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Yes
Nicolau, 2001 ³ McNabb, 2001 ⁴	Yes	No	No	No	No	Yes
Sakka, 2007 ⁵	No	Unclear or NR	No	No	No	Yes

Table B-1. Risk of bias ratings for randomized controlled trials, part 3

Author, Year Trial Name	Intermediate outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Mortality and morbidity outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Antibiotic-related adverse events assessed using valid and reliable measures, implemented consistently across all study participants?	Potential outcomes pre- specified by researchers? Are all pre-specified outcomes reported?	Risk of Bias	Comments
Nicolau, 1999 ¹	NA	NA	Unclear or NR	Yes	Medium	
Nicolau, 1999 ²	NA	NA	Unclear or NR	Yes	Medium	
Nicolau, 2001 ³ McNabb, 2001 ⁴	Yes	Yes	Yes	Yes	Medium	
Sakka, 2007 ⁵	Yes	Yes	Unclear or NR	No	High	High risk of selection bias, measurement bias, and confounding. Not blinded. It is unclear how patients were recruited and if this was different for the two different groups. It does not appear that the researchers ruled out any potential impact from a concurrent intervention or unintended exposure (several patients received various other antibiotics before receiving the treatment drug). Also all potential outcomes were not prespecified in the methods.

Observational studies

Criteria

Did the strategy for recruiting participants into the study differ across study groups?

Were groups similar at baseline?

Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?

Was overall attrition 20% or higher or was differential attrition 15% or higher?

Did attrition result in a difference in group characteristics between baseline (or randomization) and follow-up?

Did the study use intention-to-treat analysis?

Were the inclusion/ exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?

Were outcome measures equal, valid, and reliable?

Were potential outcomes pre-specified by researchers and were all pre-specified outcomes reported?

Were important confounding and modifying variables taken into account in the design and/or analysis?

Table B-2. Risk of bias ratings for observational studies, part 1

Author, Year Trial Name	Did strategy for recruiting participants into study differ across study groups?	Baseline characteristics similar between groups? If not, did analysis control for differences?	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	Was there a high rate of differential or overall attrition? (i.e., ≥20% for overall attrition or ≥15% for differential attrition)	Did attrition result in a difference in group characteristics between baseline (or randomization) and follow-up?	Is the analysis conducted on an intention-to-treat (ITT) basis?	Are the inclusion/ exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?
Lorente, 2009 ⁶	No	Yes	Unclear or NR	NA	NA	NA	Yes
Scaglione, 2009 ⁷	Unclear or NR	No	No	Unclear or NR	Unclear or NR	Unclear or NR	Yes

Table B-2. Risk of bias ratings for observational studies, part 2

Author, Year Trial Name	Intermediate outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Mortality and morbidity outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Antibiotic-related adverse events assessed using valid and reliable measures, implemented consistently across all study participants?	Potential outcomes pre- specified by researchers? Are all pre-specified outcomes reported?	Important confounding and modifying variables taken into account in the design and/or analysis?	Risk of Bias	Comments
Lorente, 2009 ⁶	Yes	Yes	NA	Yes	Yes	High	High risk of selection bias and confounding. It does not appear that the researchers ruled out any impact from a concurrent intervention or unintended exposure. Study was retrospective, not randomized, not blinded.
Scaglione, 2009 ⁷	Yes	Yes	Yes	Yes	No (Not accounted for or not identified)	High	High risk of selection bias, measurement bias, and confounding. Significant differences between groups at baseline, methods unclear, potential confounding not accounted for, outcomes reported do not map to the definitions; combined "leaving against medical advice" with mortality.

References for Appendix B

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Appendix C. Excluded Studies

Not Available in English

Shiba K, Hori S, Shimada J, Yoshida M, Saito A and Sakai O. Fundamental and clinical studies on tazobactam/piperacillin. *Chemotherapy*; 1994. p. 369-80.

Does Not Report Outcomes of Interest for this Review

Bassetti M, Righi E, Fasce R, Molinari MP, Rosso R, Di Biagio A, Mussap M, Pallavicini FB and Viscoli C. Efficacy of ertapenem in the treatment of early ventilator-associated pneumonia caused by extended-spectrum beta-lactamase-producing organisms in an intensive care unit. *J Antimicrob Chemother*. 2007 Aug;60(2):433-5. PMID: 17540673.

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Furtado GH, Gales AC, Perdiz LB, Santos AF and Medeiros EA. Prevalence and clinical outcomes of episodes of ventilator-associated pneumonia caused by SPM-1-producing and non-producing imipenem-resistant *Pseudomonas aeruginosa*. *Rev Soc Bras Med Trop*. 2011 Oct;44(5):604-6. PMID: 22031077.

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Appendix D. Evidence Tables

Table D-1. Characteristics of included studies

Author, Year Country	Study Type	Group Sample Sizes	Setting Intervention Duration Study Duration	Inclusion Criteria	Exclusion Criteria	Funding Source
Lorente, 2009 ¹ Spain	Retrospective cohort	Enrolled: 83 G1: 37 G2: 46 Analyzed: 83 G1: 37 G2: 46	ICU NR 5 years	The clinical histories of patients with VAP caused by Gram negative bacteria who received initial empirical antibiotic therapy with piperacillin/tazobactam over a 5-year period (June 2002 to December 2007) were retrieved from the patient database of the ICU. All of the following criteria had to be met for a diagnosis of VAP: chest radiography indicating new or progressive infiltrate; new onset of purulent sputum or a change in sputum character; body temperature >38 °C or <35.5 °C; white blood cell count >10,000 cells/mm ³ or <4000 cells/mm ³ ; and a significant quantitative pathogen culture from respiratory secretions (tracheal aspirate >10 ⁶ colony forming units/mL) or isolation of the same microorganism in blood and respiratory secretions. The respiratory microbiological surveillance protocol in the ICU included obtaining tracheal aspirate at intubation, twice weekly thereafter, at extubation and just before administration of empirical antibiotic therapy.	Criteria for exclusion from the study were: age <18 years; pregnancy or lactation; allergy to beta-lactam antibiotics; VAP caused by Gram-negative bacteria resistant to piperacillin/tazobactam; AIDS; neutropenia (<1000 cells/mm ³); solid or haematological tumour; and CLCr <60 mL/min by the Cockcroft–Gault equation.	Academic

Table D-1. Characteristics of included studies (continued)

Author, Year Country	Study Type	Group Sample Sizes	Setting Intervention Duration Study Duration	Inclusion Criteria	Exclusion Criteria	Funding Source
Nicolau, 1999 ² US	RCT: parallel, not clustered	Randomized: 41 G1: NR G2: NR Analyzed: 34 G1: 17 G2: 17	ICU 24 hours NR	Patients aged ≥ 18 years who were hospitalized for at least 72 hours prior to diagnosis were considered eligible when suspected of having bacterial pneumonia based on clinical evidence. Patients had to meet either A or B of the following criteria: A. Rales or dullness to percussion on physical examination of chest and any of the following: new onset of purulent sputum or change in character of sputum; organism isolated from blood culture with no apparent source other than the respiratory tract, or the same isolate recovered from blood and sputum; isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or lung biopsy; B. Chest radiographic examination shows new or progressive infiltrate, consolidation, cavitation or pleural effusion and any of the following: new onset of purulent sputum or change in character of sputum; organism isolated from blood culture; isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing or biopsy; histopathological evidence of pneumonia.	NR	Pharmaceutical

Table D-1. Characteristics of included studies (continued)

Author, Year Country	Study Type	Group Sample Sizes	Setting Intervention Duration Study Duration	Inclusion Criteria	Exclusion Criteria	Funding Source
Nicolau, 1999 ³ US	RCT: parallel, not clustered	Randomized: NR G1: NR G2: NR Analyzed: 24 G1: 13 G2: 11	ICU 24 hours NR	Patients aged ≥ 18 years who were hospitalized for ≥ 72 hours, clinically suspected of having bacterial pneumonia. Patients must have met one of two criteria: 1. Rales or dullness to percussion upon physical examination of the chest and either a) a new onset of purulent sputum or change in the character of sputum; b) an organism isolated from blood culture with no apparent source other than the respiratory tract, or the same isolate is recovered from blood and sputum; or c) the isolation of a pathogen from a specimen obtained by transtracheal aspirate, bronchial brushing, or lung biopsy; or 2. Chest radiographic examination showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion and either a) a new onset of purulent sputum or change in character of sputum; b) an organism isolated from blood culture; c) the isolation of a pathogen from a specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy; or d) histopathologic evidence of pneumonia.	NR	Pharmaceutical

Table D-1. Characteristics of included studies (continued)

Author, Year Country	Study Type	Group Sample Sizes	Setting Intervention Duration Study Duration	Inclusion Criteria	Exclusion Criteria	Funding Source
Nicolau, 2001 ⁴ McNabb, 2001 ⁵ US	RCT: parallel, not clustered	Randomized: 41 G1: NR G2: NR Analyzed: 35 G1: 18 G2: 17	ICU Mean duration of therapy in days (SD): Ceftazidime: G1: 10.0 (3.4) G2: 9.8 (3.1) Tobramycin: G1: 9.1 (3.5) G2: 9.4 (3.5) Study duration: NR	Patients 18 years of age who were hospitalized for at least 72 hours prior to diagnosis of nosocomial acquired pneumonia were considered eligible, when clinically suspected of having a bacterial aetiology. Patients must have met one of the following criteria: (1) rales or dullness to percussion on physical examination of chest and any of the following: (a) new onset of purulent sputum or change in character of sputum; (b) organism isolated from blood culture with no apparent source other than the respiratory tract or the same isolate is recovered from blood and sputum; (c) isolation of pathogen from a specimen obtained by transtracheal aspirate, bronchial brushing, or lung biopsy; or (2) chest radiographic examination showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion and any of the following: (a) new onset of purulent sputum or change in character of sputum; (b) organism isolated from blood culture; (c) isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy; (d) histopathological evidence of pneumonia.	Patients were not eligible if they were diagnosed as having AIDS, neutropenia (absolute neutrophil count 1000 cells/mm ³) or had a history of documented allergy to beta-lactam antibiotics. Similarly, patients were excluded if the signs and symptoms of pneumonia were present at the time of admission, initial APACHE II score of 25, pregnancy determined by serum – HCG testing at enrollment, or significant renal dysfunction as defined by a serum creatinine 2.5 mg/dl after appropriate fluid resuscitation or a calculated CLCr of 20 ml/min. In addition, patients with documented active tuberculosis, cystic fibrosis, viral pneumonia, infection with a microorganism known to be resistant to study medication, or those with antimicrobial therapy with activity against suspected pathogen for more than 48 hours prior to enrollment without a persistently positive culture, were not eligible.	Pharmaceutical

Table D-1. Characteristics of included studies (continued)

Author, Year Country	Study Type	Group Sample Sizes	Setting Intervention Duration Study Duration	Inclusion Criteria	Exclusion Criteria	Funding Source
Sakka, 2007 ⁶ Germany	RCT: parallel, not clustered	Randomized: 20 G1: 10 G2: 10 Analyzed: 20 G1: 10 G2: 10	ICU 3 days NR	ICU acquired pneumonia (duration of endotracheal intubation and mechanical ventilation of > 3 days) and normal renal function. Pneumonia was defined as the presence of infiltrates in the chest X-ray and positive microbiology tests for bacteria in tracheal or bronchial secretions.	Renal replacement therapy	Pharmaceutical
Scaglione, 2009 ⁷ Italy	Prospective cohort	Enrolled: 638 G1: 205 G2: 433 Analyzed: 638 G1: 205 G2: 433	PK/PD program within Hospital NR NR	Patients receiving IV aminoglycosides, fluoroquinolones, or beta lactams; and at least two of the following: cough, purulent sputum, auscultatory findings of pneumonia, dyspnea, tachypnea or pyoxemia; AND at least two of the following: fever or hypothermia, SBP <90 mm Hg, cardiac frequency ≥120 beat/min, respiratory frequency >30 breath/min, altered mental status, total peripheral white blood cell count > 10,000 cells/μL-1 , or 4,500 cells/μL-1 or >15% immature neutrophils or adequate sputum specimens for Gram stain and culture; Radiographic findings of pneumonia and life expectancy ≥ 7 days	Known or suspected meningitis, endocarditis, osteomyelitis, lung cancer or other malignancy metastatic to the lung; cystic fibrosis; suspected active tuberculosis; HIV-positive infection; liver disease and total bilirubin more than five times the upper limit of normal; severe neutropenia (<500 cells μL-1; pregnancy ALSO- to reduce variability, patients with evidence of sepsis with hypotension and/or end-organ dysfunction, shock, vasopressors required for >4 hour, duration of mechanical ventilation > 5 days or sever renal impairment requiring dialysis excluded PLUS - due to inclusion meds, patients with staphylococcal infections excluded	Government

Abbreviations: AIDS, acquired immune deficiency syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II; CLCr, creatinine clearance; G1, group 1; G2, group 2; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; ICU, intensive care unit; IV, intravenous; mL, milliliter; mm³, cubic millimeters; NR, not reported; SBP, systolic blood pressure; μL, microliter; VAP, ventilator-associated pneumonia

Table D-2. Characteristics of samples from included studies

Author, Year	Population Intervention and Comparator Groups	Baseline Severity of Illness [mean (SD)]	Age [mean (SD)]	% Female	% Nonwhite	Other Baseline Characteristics
Lorente, 2009 ¹	VAP G1: Continuous infusion G2: Intermittent infusion	APACHE II score G1: 16.1 (2.09) G2: 16.2 (2.15) SOFA score at suspicion of VAP [mean (SD)] G1: 9.1 (2.23) G2: 8.8 (2.06) p=0.57	G1: 63.2 (9.76) G2: 61.8 (9.91)	G1: 21.6% G2: 21.7%	NR	COPD (N) G1: 5 G2: 5 p=0.75 Creatinine clearance [mean mL/min (SD)]: G1: 102.2 (14.54) G2: 101.3 (11.80) p=0.75 Vasopressor use [N (%)]: Overall: NR G1: 26 (70.3) G2: 29 (63.0) p= 0.64 Steroid use [N (%)] Overall: NR G1: 14 (37.8) G2: 15 (32.6) p=0.65
Nicolau, 1999 ²	Nosocomial pneumonia G1: Intermittent infusion G2: Continuous infusion	APACHE II score: G1: 15 (4) G2: 14 (4)	G1: 51 (21) G2: 43 (15)	G1: 29% G2: 41%	NR	Estimated creatinine clearance [mean (SD)]: G1: 92 (38) G2: 102 (30)
Nicolau, 1999 ³	Nosocomial pneumonia G1: Intermittent infusion G2: Continuous infusion	APACHE II score: G1: 14.5 (4.7) G2: 13.8 (5.0)	G1: 45 (18.7) G2: 36.5 (13.2)	G1: 38% G2: 36%	NR	Days from admission to initiation of therapy [median (range)]: G1: 8 (4-20) G2: 7 (3-26) Creatinine clearance [mean (SD)]: G1: 100 (38) G2: 104 (32)

Table D-2. Characteristics of samples from included studies (continued)

Author, Year	Population Intervention and Comparator Groups	Baseline Severity of Illness [mean (SD)]	Age [mean (SD)]	% Female	% Nonwhite	Other Baseline Characteristics
Nicolau, 2001 ⁴ McNabb, 2001 ⁵	Nosocomial pneumonia G1: Intermittent infusion G2: Continuous infusion	APACHE II score: G1: 15.5 (6.3) G2: 13.9 (4.4) p=0.426	G1: 56 (20) G2: 46 (16) p=0.104	G1: 28% G2: 41% p=0.404	NR	Ventilated at baseline (N): G1: 16 G2: 16 p= 0.581 Comorbidites [N (%]): COPD G1: 1 (6) G2: 0 (0) Cardiovascular disease G1: 9 (50) G2: 5 (29) Alcoholism G1: 6 (33) G2: 4 (24) Diabetes mellitus G1: 3 (17) G2: 2 (12) Cancer G1: 2 (11) G2: 1 (6) Systolic BP<=90 mm Hg G1: 2 (11) G2: 2 (12) Serum creatinine >=1.7 mg/dl G1: 0 (0) G2: 1 (6) Immunosuppression (steroids) G1: 4 (22) G2: 4 (24) History of smoking G1: 4 (22) G2: 2 (12)

Table D-2. Characteristics of samples from included studies (continued)

Author, Year	Population Intervention and Comparator Groups	Baseline Severity of Illness [mean (SD)]	Age [mean (SD)]	% Female	% Nonwhite	Other Baseline Characteristics
Sakka, 2007 ⁶	ICU-acquired pneumonia G1: Continuous infusion G2: Intermittent infusion	APACHE II score G1: 26 (6) G2: 28 (5) SOFA score G1: 7 (2) G2: 6 (3) SAPS II score G1: 44 (14) G2: 43 (12)	G1: 62 (16) G2: 59 (16)	G1: 40 G2: 50	NR	Height [mean cm (SD)]: G1: 171 (8) G2: 170 (7) Weight [mean kg (SD)]: G1: 73 (8) G2: 78 (14) BSA [mean m ² (SD)]: G1: 1.84 (0.14) G2: 1.89 (0.16) Creatinine clearance [mean ml/min (SD)]: G1: 122 (33) G2: 128 (35)
Scaglione, 2009 ⁷	Nosocomial pneumonia G1: Patients with drug concentration and isolate MIC available G2: Patients lacking drug concentration, isolate MIC, or both	APACHE II score G1: 17.8 (5.0) G2: 19.02 (4.6) Nosocomial Pneumonia with Bacteremia [N (%)] G1: 33 (16.1%) G2: 18 (4.16%) Nosocomial Pneumonia only [N (%)] G1: 172 (83.9%) G2: 415 (95.84%) p<0.001	G1: 67 (8) G2: 69 (8)	NR	NR	NR

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BP, blood pressure; BSA, body surface area; cm, centimeters; COPD, chronic obstructive pulmonary disease; G1, group 1; G2, group 2; ICU, intensive care unit; kg, kilogram; m², meters squared; mg/dL, milligrams per deciliter; MIC, minimum inhibitory concentration; mm HG, millimeters of mercury; SAPS II, Simplified Acute Physiology Score II; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; VAP, ventilator-associated pneumonia

Table D-3. Intervention and comparator components from included studies

Author, Year	Intervention Type	Description of Intervention	Comparator Type	Description of Comparator
Lorente, 2009 ¹	Prolonged or continuous infusion	Piperacillin 4g/tazobactam 0.5g infused over 360 min every 6 hours, following a loading dose of 4g piperacillin/0.5g tazobactam infused over 30 min	Bolus dosing	Piperacillin 4g/tazobactam 0.5g infused over 30 min every 6 h
Nicolau, 1999 ²	Prolonged or continuous infusion	Ceftazidime 3g administered over 24 h using an infusion pump, following 1g bolus dose administered over 30 min at initiation of treatment Dosages adjusted for body weight >100 kg and renal dysfunction	Bolus dosing	Ceftazidime 2g administered over 30 min every 8 hours Dosages adjusted for body weight >100 kg and renal dysfunction
Nicolau, 1999 ³	Prolonged or continuous infusion	Ceftazidime 3g administered over 24 h using an infusion pump, following 1g bolus dose administered over 30 min at initiation of treatment	Bolus dosing	Ceftazidime 2g administered over 30 min every 8 hours
Nicolau, 2001 ⁴ McNabb, 2001 ⁵	Continuous infusion	Ceftazidime 3g administered over 24 h using an infusion pump, following 1g bolus dose administered over 30 min at initiation of treatment Dosages adjusted for body weight >100 kg and renal dysfunction	Bolus dosing	Ceftazidime 2g administered over 30 min every 8 hours Dosages adjusted for body weight >100 kg and renal dysfunction
Sakka, 2007 ⁶	Continuous infusion	Continuous imipenem 7g/cilastatin 7g administered over 72 h, following a loading dose of of imipenem 1g/cilastatin 1g as a short-term infusion	Bolus dosing	Intermittent Imipenem 1g/cilastatin 1g 3times daily for 3 days; 9 infusions within 72 h
Scaglione, 2009 ⁷	Serum concentration	Patients with drug concentration and isolate MIC available	Serum concentration (other) or no use of PK/PD measures	Patients lacking drug concentration, isolate MIC, or both

Abbreviations: g, grams; min, minutes; h, hours; kg, kilograms; MIC, minimum inhibitory concentration

Table D-4. Clinical response and mechanical ventilation outcomes

Author, Year	Intervention and Comparator Groups	Clinical Response – Definition	Clinical Response – Results	Mechanical Ventilation – Definition	Mechanical Ventilation – Results
Lorente, 2009 ¹	G1: Piperacillin/tazobactam continuous infusion G2: Piperacillin/tazobactam intermittent infusion	NR	NR	NR	NR
Nicolau, 1999 ²	G1: Ceftazidime intermittent infusion (N=17) G2: Ceftazidime continuous infusion (N=17)	NR	NR	NR	NR
Nicolau, 1999 ³	G1: Ceftazidime intermittent infusion (N=13) G2: Ceftazidime continuous infusion (N=11)	NR	NR	NR	NR
Nicolau, 2001 ⁴ McNabb, 2001 ⁵	G1: Ceftazidime intermittent infusion (N=18) G2: Ceftazidime continuous infusion (N=17)	Clinical outcome: clinical cure or improvement versus clinical failure Clinical cure — complete resolution of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on the chest radiograph Clinical improvement—improvement of signs and symptoms of pneumonia, with evidence of infection remaining;	Clinical outcome: p=0.592 Clinical cure [N (%): G1: 6 (33) G2: 7 (41) Clinical improvement [N (%): G1: 9 (50) G2: 9 (53) Clinical failure [N (%): G1: 3 (17) G2: 1 (6)	Duration of mechanical ventilation during enrollment in days	Duration of mechanical ventilation [mean days (SD)] G1: 8.3 (4.3) G2: 7.9 (4.0) p=0.970

Table D-4. Clinical response and mechanical ventilation outcomes (continued)

Author, Year	Intervention and Comparator Groups	Clinical Response – Definition	Clinical Response – Results	Mechanical Ventilation – Definition	Mechanical Ventilation – Results
Sakka, 2007 ⁶	G1: Continuous imipenem/cilastatin (N=10) G2: Intermittent imipenem/cilastatin (N=10)	NR	NR	NR	NR
Scaglione, 2009 ⁷	G1: Patients with drug concentration and isolate MIC available (N=205) G2: Patients lacking drug concentration, isolate MIC, or both (N=433)	Clinical cure - Absence or improvement of clinically significant symptoms and signs such that no additional therapy was required Clinical failure -Persistence or progression of symptoms and signs or death of the patient	Clinical cure (N): G1: 168 G2: 293 Clinical failure (N): G1: 37 G2: 140 p<0.001	Number requiring mechanical ventilation Duration of mechanical ventilation in days	Number requiring mechanical ventilation: G1: 25 G2: 52 Duration of mechanical ventilation [mean days (SD)] G1: 4.28 (1.3) G2: 5.39 (1.8) p=0.09

Abbreviations: G1, group 1; G2, group 2; MIC, minimum inhibitory concentration ; N, number; p, p-value; SD, standard deviation

Table D-5. Morbidity and mortality outcomes

Author, Year	Intervention and Comparator Groups	Mortality – Definition	Mortality – Results	Morbidity – Definition	Morbidity – Results
Lorente, 2009 ¹	G1: Piperacillin/ tazobactam continuous infusion G2: Piperacillin/ tazobactam intermittent infusion	NR	NR	NR	NR
Nicolau, 1999 ²	G1: Ceftazidime intermittent infusion (N=17) G2: Ceftazidime continuous infusion (N=17)	NR	NR	NR	NR
Nicolau, 1999 ³	G1: Ceftazidime intermittent infusion (N=13) G2: Ceftazidime continuous infusion (N=11)	NR	NR	NR	NR
Nicolau, 2001 ⁴ McNabb, 2001 ⁵	G1: Ceftazidime intermittent infusion (N=18) G2: Ceftazidime continuous infusion (N=17)	NR	NR	Superinfection with methicillin-resistant S. aureus	Superinfection [N]: G1: 1 G2: 0
Sakka, 2007 ⁶	G1: Continuous imipenem/ cilastatin (N=10) G2: Intermittent imipenem/ cilastatin (N=10)	All-cause mortality	Mortality [N]: G1: 1 G2: 2	NR	NR
Scaglione, 2009 ⁷	G1: Patients with drug concentration and isolate MIC available (N=205) G2: Patients lacking drug concentration, isolate MIC, or both (N=433)	All-cause mortality or patient left the hospital against medical advice	Mortality [N (%)] G1: 21 (10.24%) G2: 102 (23.55%) p<0.001	NR	NR

Abbreviations: G1, group 1; G2, group 2; MIC, minimum inhibitory concentration; N, number; p, p-value

Table D-6. Antibiotic-related adverse events

Author, Year	Intervention and Comparator Groups	Organ Toxicity – Definition	Organ Toxicity – Results	Hemato-logical Effects – Definition	Hemato-logical Effects – Results	C. difficile Infection – Definition	C. difficile Infection - Results	Antibiotic Resistance – Definition	Antibiotic Resistance – Results	Other Adverse Effects – Definition	Other Adverse Effects - Results
Lorente, 2009 ¹	G1: Piperacillin/ tazobactam continuous infusion G2: Piperacillin/ tazobactam intermittent infusion	NR	NR	NR	NR	NR	NR	Antibiotic resistance developing during the course of treatment	N with outcome: G1: 0 G2: 0	NR	NR
Nicolau, 1999 ²	G1: Ceftazidime intermittent infusion (N=17) G2: Ceftazidime continuous infusion (N=17)	NR	NR	NR	NR	NR	NR	NR	NR	Infusion- related adverse effects (e.g. phlebitis)	N with outcome: G1: 0 G2: 0
Nicolau, 1999 ³	G1: Ceftazidime intermittent infusion (N=13) G2: Ceftazidime continuous infusion (N=11)	NR	NR	NR	NR	NR	NR	NR	NR	Adverse effects related to the dosing regimen of ceftazidime	N with outcome: G1: 13 G2: 11

Table D-6. Antibiotic-related adverse events (continued)

Author, Year	Intervention and Comparator Groups	Organ Toxicity – Definition	Organ Toxicity – Results	Hemato-logical Effects – Definition	Hemato-logical Effects – Results	C. difficile Infection – Definition	C. difficile Infection - Results	Antibiotic Resistance – Definition	Antibiotic Resistance – Results	Other Adverse Effects – Definition	Other Adverse Effects – Results
Nicolau, 2001 ⁴ McNabb, 2001 ⁵	G1: Ceftazidime intermittent infusion (N=18) G2: Ceftazidime continuous infusion (N=17)	Nephro-toxicity related to tobramycin	N with outcome: G1: 2 G2: 1	NR	NR	C. difficile infection reported at any time during study duration	N with outcome: G1: 1 G2: 2	Greater than twofold increase in MIC compared with that of the initial determination (i.e. enrollment specimen)	N with outcome: G1: 18 G2: 17	NR	NR
Sakka, 2007 ⁶	G1: Continuous imipenem/cilastatin (N=10) G2: Intermittent imipenem/cilastatin (N=10)	NR	NR	NR	NR	NR	NR	NR	NR	Imipenem-related adverse reactions (i.e. seizures)	N with outcome: G1: 0 G2: 0
Scaglione, 2009 ⁷	G1: Patients with drug concentration and isolate MIC available (N=205) G2: Patients lacking drug concentration, isolate MIC, or both (N=433)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: C. difficile, clostridium difficile; G1, group 1; G2, group 2; MIC, minimum inhibitory concentration ; N, number

References for Appendix D

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