Effective Health Care Program

Comparative Effectiveness Review
Number 136

Pharmacokinetic/ Pharmacodynamic Measures for Guiding Antibiotic Treatment for Hospital-Acquired Pneumonia

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Pharmacokinetic/Pharmacodynamic Measures for Guiding Antibiotic Treatment for Hospital-Acquired Pneumonia

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This report is based on research conducted by the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2012-00008-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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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 email 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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The authors deeply appreciate the considerable support, commitment, and contributions of the EPC team staff at the RTI–UNC EPC. We express our gratitude to the following individuals for their contributions to this project: Loraine Monroe and Sharon Barrell, M.A., of RTI, and Jennifer Middleton, Ph.D., of UNC.

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Before publication of the final evidence report, the RTI-UNC EPC sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Pharmacokinetic/Pharmacodynamic Measures for Guiding Antibiotic Treatment for Hospital-Acquired Pneumonia

Structured Abstract

Objective. 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 adults with hospital-acquired pneumonia (HAP).

Data sources. MEDLINE® (via PubMed), Cochrane Library, International Pharmaceutical Abstracts, and ClinicalTrials.gov from January 1, 2004, to June 7, 2014.

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

Results. Ten studies (seven trials, three 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 either intermediate or health outcomes. One trial (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 HAP, 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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Background

Hospital-Acquired Pneumonia: Epidemiology

Hospital-acquired (or nosocomial) pneumonia (HAP) is the second most common hospital-acquired infection. It occurs 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) described HAP and two related pneumonias, ventilator-associated pneumonia (VAP) and healthcare-associated pneumonia (HCAP).[1] Briefly:

- HAP is a pneumonia that occurs 48 hours or more after admission and was not incubating at the time of admission.
- VAP is a pneumonia that presents more than 48 to 72 hours after endotracheal intubation. It is a severe type of HAP; because of the difficulty in treating it, its prognosis can be poor.
- HCAP is a pneumonia that develops in any patient who meets one or more of several criteria: had been hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; had resided in a nursing home or long-term care facility; had received recent intravenous (IV) antibiotic therapy, chemotherapy, or wound care within the 30 days preceding the current infection; or had attended a hospital or hemodialysis clinic.

Unless we specify otherwise, the term "HAP" includes VAP and HCAP throughout the report. Most biological and clinical principles for HAP and VAP overlap those for HCAP.

HAP is most often caused by bacterial pathogens, and it may be polymicrobial. *Staphyloccus aureus*—especially methicillin-resistant *S. aureus* (MRSA)—and aerobic Gram-negative bacilli, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* species, are the common causes of HAP. 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.[1,5]

Because HAP, VAP, and HCAP share similar microbial sources, they are treated similarly. The general approach is to treat broadly for resistant Gram-positive and Gram-negative organisms, then deescalate therapy when the pathologic agent is defined. 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 treat them in ways similar to those used for treating patients with VAP.

HAP is associated with increased morbidity and mortality, longer lengths of inpatient stays, and higher costs of care compared with hospital episodes not complicated by HAP 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 HAP; 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.[6] Additional costs per episode of VAP may be as high as $40,000.[7]

Hospital-Acquired Infection: Treatment

Appropriate antibiotic therapy significantly improves survival for patients with HAP.[8-11] Relevant antibiotics for treating HAP patients include broad-spectrum beta-lactams, vancomycin, and aminoglycosides, among others. Table A lists antibiotic classes and individual agents that clinicians might use 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 Subclass	Drug[a]
Aminoglycosides	NA	**Gentamicin[a]** **Tobramycin[a]** **Amikacin[a]**
Beta-lactams	Penicillins	Penicillin G Oxacillin Nafcillin
	Beta-lactam/beta-lactamase inhibitors	Ampicillin/sulbactam **Piperacillin/tazobactam[a]** **Ticarcillin/clavulanic acid[a]**
	Cephalosporins	Cefazolin Ceftriaxone Cefotaxime **Ceftazidime[a]** **Cefepime[a]** Ceftaroline
	Monobactams	**Aztreonam[a]**
	Carbapenems	**Doripenem[a]** Ertapenem **Imipenem[a]** **Meropenem[a]**
Fluoroquinolones	NA	Levofloxacin Ciprofloxacin Moxifloxacin
Glycopeptides	NA	**Vancomycin[a]**
Glycylcyclines	NA	Tigecycline
Oxazolidinone	NA	**Linezolid[a]**
Polymyxin	NA	Colistin (also called colistimethate sodium)
Rifamycins	NA	Rifampin Rifampicin
Tetracyclines	NA	Doxycycline Minocycline

NA = not applicable; PK/PD = pharmacokinetic/pharmacodynamic.
[a]Drug names in bold represent intravenous antibiotics most commonly used to treat hospital-acquired pneumonia.

Optimal treatment involves choosing the right drug or combination of drugs, the proper dose and route of administration, and the appropriate duration, followed by deescalation to pathogen-

directed therapy.[1] Subtherapeutic dosing of antibiotics has been associated with poorer clinical outcomes and emergence of antibiotic resistance.[12-15]

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.[16] 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 specifically for HAP, the 2005 ATS/IDSA guidelines recommend 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. This antibiotic dosing logic is based on serum antibiotic concentrations in vitro and in vivo observations. For those reasons, it may not account fully 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.

Furthermore, measuring PK/PD only in the serum may lead to suboptimal antibiotic concentrations at the site of infection—in this case, the lung. In such cases, the antibiotic may not eradicate resistant organisms; this problem may in turn lead to treatment failure and contribute to emerging antibiotic resistance. Generally speaking, given the unique attributes of the lung that contribute to the challenge of adequately treating patients with HAP, these issues are of special concern for clinicians and others in providing fully successful services for such patients.

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.[17,18] 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 three decades. During the same period, the number of new antibiotics developed has decreased, especially for drugs that target Gram-negative organisms. In addition, treatment of MRSA pneumonia has become more difficult because of the rising incidence of infections caused by isolates with increased MICs to vancomycin ("MIC creep"). To reach proposed pharmacodyamic targets, higher doses of vancomycin are needed, which increases risks of toxicities.[19] With fewer antibiotic options, ensuring the appropriate and judicious use of these drugs becomes increasingly important.[20,21]

Although optimization of antibiotic dosing is important to improve individual patient outcomes with HAP, 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 have important implications, not only for the individual patient being treated, but also for public health concerns.

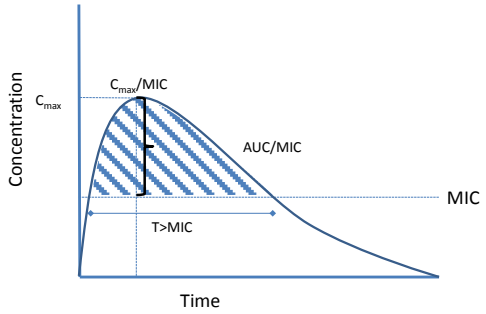
Scope and Key Questions

Scope of This Review

This review aims to document the impact of contemporary approaches to PK/PD-guided dosing of 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 curve (AUC) for the concentration-time curve in relationship to MIC (expressed as AUC/MIC)

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



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 = 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 include 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 and use of ventilators) and health outcomes (morbidity and mortality); we also examined evidence about adverse events (harms). We examined evidence relating to HAP 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 HAP 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 PD properties of different IV antibiotics, 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. The review 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 populations, interventions, comparators, outcomes, timing of measurement or followup, and settings (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 for 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 HAP patients. Finally, we excluded studies in which serum concentration had been measured without comparing different serum concentration targets; 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 Figure 2 of the full report.

Key Question 1. For people with hospital-acquired 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 hospital-acquired 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. For people with hospital-acquired pneumonia, 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 when examining the use of PK/PD measures to inform decisions about dosing and monitoring antibiotic treatment or when comparing prolonged or continuous infusions versus bolus infusions for beta-lactams?

Methods

Our protocol for this review was registered with PROSPERO (CRD42013005309).

Literature Search Strategy

Search Strategy

We searched MEDLINE® (via PubMed), the Cochrane Library, and the International Pharmaceutical Abstracts for English-language and human-only studies from January 1, 2004, through May 15, 2013; we later updated the searches through June 7, 2014. 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 Technical Expert Panel members and incorporated their input into our search strategies. An experienced information scientist, our Evidence-based Practice Center (EPC) librarian, ran the searches; another EPC librarian peer-reviewed the searches.

We manually searched reference lists of pertinent reviews and included trials, and searched 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, 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, and ratio of AUC to MIC. For KQ 2, we required studies to compare prolonged or continuous infusions with bolus infusions for beta-lactams. (As noted above, the clinical concern for this review is the lung and specifically pneumonia, so studies about other types of infections or infections in other organ systems are excluded.)

For KQs 1 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 KQs 2 and 3, the eligible comparator was 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, *Clostridium difficile* infection, antibiotic resistance). No limits were placed on timing of the measurement or followup. HAP had to have begun in a health care setting (e.g., skilled nursing facility) and be treated in the hospital (e.g., emergency department, floor, or ICU).

For both intermediate and health outcomes, randomized controlled trials (RCTs), nonrandomized controlled trials, and 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. Studies whose titles and abstracts 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 recorded relevant data from the studies; 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., the internal validity) of studies, we applied predefined criteria based on the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (Methods Guide).[22] 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.[23] 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 independently 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. Reviewers can assign one of four strength-of-evidence grades: high, medium, low, or insufficient. For the last, evidence either is unavailable or does not permit estimation of an effect.

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 both individual studies and the body of evidence following guidance from the AHRQ Methods Guide.[24] 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.

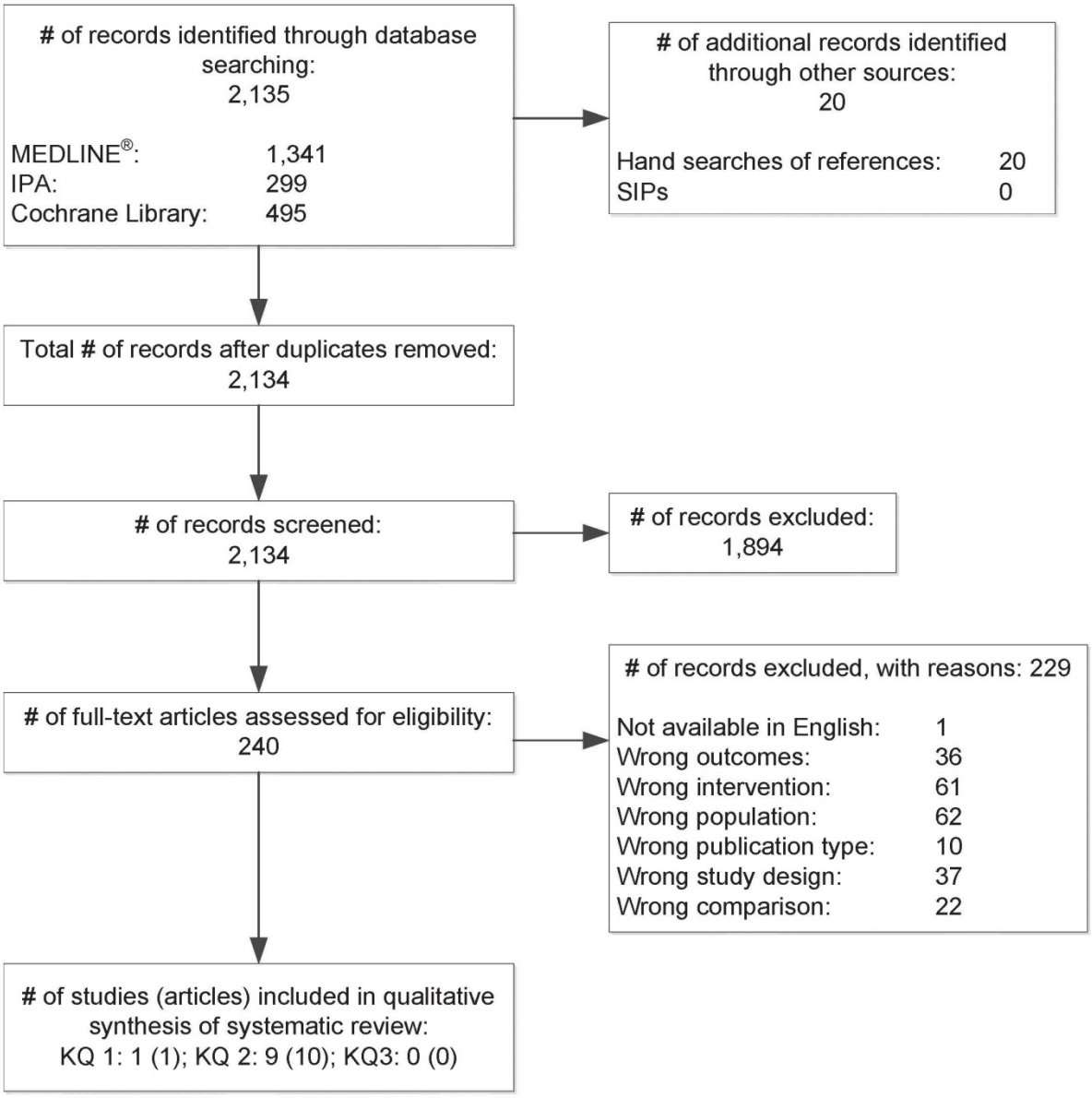
Results

Results of Literature Searches

From an unduplicated pool of 2,134 possible articles, we excluded 1,894 at the title and abstract review stage and another 240 at the full-text review stage (Figure B). We included 10 studies reported in 11 published articles. Of these, one study pertained to KQ 1; nine pertained to KQ 2. We identified no studies addressing KQ 3, on subgroups.

Seven studies were RCTs.[25-32] Two were prospective cohort studies,[33,34] and one was a retrospective cohort study.[35] All seven RCTs addressed KQ 2. One prospective cohort study pertained to KQ 1[33] and the other to KQ2[34]; the retrospective cohort study addressed KQ 2. We rated five the trials and one cohort study as medium risk of bias and two trials and two cohort studies as high risk of bias.

Figure B. Disposition of articles about using PK/PD measures in hospital-acquired pneumonia



IPA=International Pharmaceutical Abstracts; KQ = Key Question; PK/PD = pharmacokinetic/pharmacodynamic; SIP = Scientific Information Packet

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 that we rated as high risk of bias for multiple reasons, including high risk of measurement bias and confounding. Further, methods were not clearly described. Investigators reported significantly improved outcomes with PK/PD in terms of cure and mortality, but both measures were problematic.[33] Whether the data reported were based on clinical or microbiologic success data (or both) was unclear, 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	Precise	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	Precise	Insufficient

AMA = against medical advice; 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. We had no more than one study for any included outcome, and this small number of studies had small numbers of patients. These problems generally resulted 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.[26,28] Evidence is also insufficient to draw conclusions about the effect of continuous infusions versus intermittent infusions on the rates of antibiotic-related adverse events.[25-29,35]

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

Outcome Category	Outcome	No. of Studies (Subjects)	Risk of Bias	Consis-tency	Direct-ness	Precision	Overall Strength of Evidence
Intermediate outcomes	Clinical response	3 RCTs (n=96)	Medium	Consis-tent	Direct	Imprecise	Insufficient
		1 prospective cohort (n=61)	Medium	NA	Direct	Imprecise	
	Mechanical ventilation	2 RCTs (n=66)	Medium	Consis-tent	Direct	Imprecise	Insufficient
		1 prospective cohort (n=61)	Medium	NA	Direct	Imprecise	
	Treatment failure	1 RCT (n=35)	Medium	NA	Direct	Imprecise	Insufficient
Morbidity and mortality outcomes	Superinfection	2 RCTs (n=66)	Medium	Inconsis-tent	Indirect	Imprecise	Insufficient

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

Outcome Category	Outcome	No. of Studies (Subjects)	Risk of Bias	Consis-tency	Direct-ness	Precision	Overall Strength of Evidence
Antibiotic-related adverse events	Organ toxicity	1 RCT (n=35)	Medium	NA	Indirect	Imprecise	Insufficient
	Hematologic effects	0 (0)	NA	NA	NA	NA	NA
	C. difficile infection	1 RCT (n=35)	Medium	NA	Direct	Imprecise	Insufficient
	Antibiotic resistance	1 RCT (n=35)	Medium	Consis-tent	Direct	Imprecise	Insufficient
		1 retrospective cohort (n=83)	High	NA	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
	Adverse events attributed to the dosing regimen of doripenem	1 RCT (n=NR)	High	NA	Unknown	Imprecise	Insufficient
	Infusion-related adverse effects (e.g., phlebitis)	1 RCT (n=34)	Medium	NA	Unknown	Imprecise	Insufficient

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

Comparative evidence is scarce on use of PK/PD measures in dosing or monitoring. Similarly, little evidence is available on use of PK/PD strategies in adult patients with HAP who are being treated with IV antibiotics.

The strength of evidence is insufficient to conclude whether using measures to inform decisions about dosing or monitoring IV antibiotic treatment (KQ 1) improves either intermediate or health outcomes. We found only a single prospective cohort study (which we 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). Pertinent studies found no significant differences in clinical response,

duration of mechanical ventilation, superinfection, rates of antibiotic-related adverse events, or infusion-related adverse effects.

We determined that very little research has focused on the use of PK/PD measures in dosing or monitoring adult patients with HAP being treated with IV antibiotics. This dearth of studies suggests that the research conducted to date has been conducted in in vitro and animal studies. In what little is published 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, HAP) without reporting outcomes for patients with HAP (including VAP and HCAP), separately. Our review focused solely on HAP and explicitly omitted community-acquired pneumonia.

Many national and international organizations have recognized the growing global problem of antibiotic resistance and have made efforts to raise public awareness and coordinate actions to address problems related to resistance. For example, the U.S. National Institutes of Health has issued new funding opportunities to encourage new antibiotic developments, and the Centers for Disease Control and Prevention has launched the Get Smart Campaign to encourage the judicious use of antibiotics. Strategies often employed include infection control and prevention techniques such as hand-washing, development of rapid point-of-care diagnostic tests to diagnose infection more rapidly and accurately, public policies to support development and approval of new drugs to treat resistant infections, and implementation of coordinated efforts to optimize antibiotic use through practices referred to as antibiotic stewardship.

Antibiotic stewardship programs have several goals. Among them are improving appropriate use of antibiotics by promoting antibiotic use only when indicated and selecting optimal antimicrobial drug regimens to improve clinical outcomes. Minimizing toxicity and other adverse events, including limiting the emergence of antibiotic-resistant strains of bacteria, is a related goal. Such programs often focus on streamlining antimicrobial therapy, deescalating or targeting antibiotics based on microbiological data, minimizing excessive durations of antibiotic courses, and optimizing antibiotic doses.

The IDSA, the Society for Healthcare Epidemiology of America, and the Pediatric Infectious Diseases Society have all made recommendations to the Centers for Medicare & Medicaid Services to require antibiotic stewardship programs in all acute care hospitals in the United States.[36] Pharmacodynamic dose optimization has been suggested as a strategy for antibiotic stewardship programs to employ to improve antibiotic use.[37] In fact, the IDSA guidelines for developing an institutional program to enhance antimicrobial stewardship refer to PK and PD considerations as important parts of antimicrobial stewardship.[38]

Given the dearth of findings in this review, the evidence base provides little guidance for either clinical or policy decisionmaking. We comment here on two key issues that warrant attention by health professionals, policymakers, and society at large; we offer specific recommendations about filling these research gaps below.

First, as antimicrobial resistance becomes a global problem, appropriate use of antibiotics is of paramount importance. Appropriate use encompasses optimal dosing strategies that are cost effective, can improve patient outcomes, and combat further development of resistance. These matters are relevant to clinicians, hospital administrators, insurers, patients, and public-sector agencies. With respect specifically to PK/PD approaches, of particular interest are exposure-response relationships of antibiotics, antibiotic use in "real-world" clinical settings (all types of hospitals and ICUs), and a broad range of patient-centered outcomes (clinical response, morbidity, mortality, and adverse events) as well as costs of care.

Second, almost a decade ago, 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 remains unclear. Clinicians and policymakers alike would benefit from updated information that will point to more effective strategies for using current therapies than are now widely available.

In summary, despite the theoretical advantages of optimizing IV antibiotic dosing using PK/PD principles in patients with HAP, 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 included diverse patient populations.

Research Gaps

First, whether use of PK/PD measures for informing dosing decisions for patients with HAP influences clinical outcomes remains unknown, largely because of both the absence of studies and 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 study populations were sufficiently diverse that they cannot be expected to produce "consistent" findings (and in fact did not).

Second, two key topics were not addressed in most investigations: (1) use of targeted and monitored antibiotic concentrations to tailor antibiotic doses of individual patients and (2) 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 datasets, few in vivo studies have 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—or preferably, patient-centered health outcomes, especially disease or death. In this review, only one RCT evaluated clinical outcomes in patients with HAP receiving continuous versus intermittent ceftazidime infusions.[28]

Third, the effect of optimizing antibiotic dosing based on PK/PD principles for patients with HAP who fall into various clinical or sociodemographic subgroups is not known. Specifically, 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). The gaps in understanding the links among patient-specific factors, organism MIC, antibiotic dose, and clinical outcomes reflect the difficulty in isolating these variables and establishing cause-effect relationships. Elevated organism MICs, and thus antibiotic regimen and dosing choices, may be correlated with disease severity without having a causal effect. Furthermore, unmeasured organism factors such as virulence determinants, which may be associated with elevated MICs, may play a role in patient outcomes. These potential

confounding variables should be considered when drawing conclusions about the effects of antibiotic dose optimization on patient outcomes.[39-41]

Finally, 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 MRSA 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 today's approach to antibiotic dosing, which is based on the assumptions outlined above for PK/PD. Because present dosing recommendations are based largely 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 primary goals of such investigations are (1) to document the impact of different dosing strategies on meaningful clinical and patient-centered endpoints, such as survival in different patient populations, and (2) to determine their effects on the development of antibiotic resistance in bacteria. In addition, such studies can provide important data on other outcomes of interest to both clinicians and patients; these include ventilator days, rates of relapse, rates of reinfection, mortality risk, and timeliness of laboratory results in terms of being clinically useful in managing treatment. Measuring microbiological outcomes such as eradication of bacteria, microbiologic relapse, decrease in colony counts of culture, and development of antibiotic resistance can also yield information useful for developing dosing guidelines and recommendations. For certain patient-centered outcomes, such as clinical response and treatment failure not otherwise explained, clearly identifying how the investigators defined those outcomes (e.g., clinician judgment of patient signs and symptoms, laboratory values, quality of life assessed through patient self-reports, or mortality as measured at specific points in time) will improve interpretation of the findings. We believe research teams should be precise in delineating their conceptualization of all such outcomes.

Although antibiotic resistance clearly can arise during or from antibiotic treatment, less is known about the relationships among drug dosage, PK/PD optimization, and the development of resistance. Evaluating either the development or the prevention of resistance is a difficult research endeavor. Nevertheless, investigators can institute several approaches such as monitoring resistance trends in individual patients or tracking changes in hospital or local susceptibility patterns over time. Metrics for evaluating the development of resistance should be tested and validated in relationship to meaningful clinical and ultimate health outcomes. Researchers mounting PK/PD studies would then have more reliable and valid ways to examine this very important public health concern.

Conclusions

In the setting of increasing antimicrobial resistance worldwide and limited new antibiotics in the pipeline, optimizing dosing with PK/PD strategies could serve as an important antimicrobial stewardship tool to improve the use of currently available antibiotics. While PK/PD dosing strategies are supported by concept, the lack of prospective patient outcome data leaves clinicians with little guidance on how to best apply these principles to patient care. This review

highlights the significant need for additional research to illuminate the role of antibiotic PK/PD dose optimization for the treatment of HAP.

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Introduction

Background

Hospital-Acquired Pneumonia: Epidemiology

Hospital-acquired (or nosocomial) pneumonia (HAP) is the second most common hospital-acquired infection. It occurs 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*) described HAP and two related pneumonias, ventilator-associated pneumonia (VAP) and health-care-associated pneumonia (HCAP).[1] Briefly:

- HAP is a pneumonia that occurs 48 hours or more after admission and was not incubating at the time of admission.
- VAP is a pneumonia that presents more than 48 to 72 hours after endotracheal intubation. It is a severe type of HAP; because of the difficulty in treating it, its prognosis can be poor.
- HCAP is a pneumonia that develops in any patient who meets one or more of several criteria: had been hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; had resided in a nursing home or long-term care facility; had received recent intravenous (IV) antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or had attended a hospital or hemodialysis clinic.

Unless we specify otherwise, the term "HAP" includes VAP and HCAP throughout the report. Most biological and clinical principles for HAP and VAP overlap those for HCAP.

HAP is most often caused by bacterial pathogens, and it may be polymicrobial. *Staphyloccus aureus (S. aureus)*—especially methicillin-resistant *S. aureus (MRSA*)—and aerobic Gram-negative bacilli, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* species, are the common causes of HAP. 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.[1,5]

Because HAP, VAP, and HCAP share similar microbial sources, they are treated similarly. The general approach is to treat broadly for resistant Gram-positive and Gram-negative organisms, then de-escalate therapy when the pathologic agent is defined. 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 treat them in ways similar to treating patients with VAP.

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] Gram-negative pathogens, such as *Pseudomonas aeruginosa* and *Acinetobacter* species, are of particular concern because of increasing rates of resistance and lack of effective antibiotic options for treatment. Pneumonia caused by MRSA is also a concern because of the emergence of strains with decreased susceptibility to vancomycin, reports of poor clinical outcomes, and increased risks of toxicities associated with increasing vancomycin doses.

Patients who have received mechanical ventilation are at the greatest risk for HAP; 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.[8] Additional costs per episode of VAP may be as high as $40,000.[9]

Beyond mechanical ventilation, numerous other factors may increase a patient's risk for HAP.[10-21] These variables include:

- Age >60 years
- Chronic lung disease
- Presence of various underlying illness
- Depressed consciousness
- Aspiration
- Use of acid-suppressing medications
- Use of paralytic agents
- Previous antibiotic exposure, particularly to third-generation cephalosporins
- Mechanical ventilation for acute respiratory distress syndrome
- Reintubation or prolonged intubation
- Frequent ventilator circuit changes
- Chest surgery
- Transport from the ICU for diagnostic or therapeutic procedures
- Presence of an intracranial pressure monitor or nasogastric tube
- Hospitalization during the fall or winter season

HAP Infection: Treatment

Appropriate antibiotic therapy significantly improves survival for patients with HAP.[22-25] Relevant antibiotics for treating HAP patients include broad-spectrum beta-lactams, vancomycin, and aminoglycosides, among others. Table 1 lists antibiotic classes and individual agents that clinicians might use to treat HAP; bold items are those used most often.

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

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

NA = not applicable; PK/PD = pharmacokinetic/pharmacodynamics.
[a]Drug names in bold represent intravenous antibiotics most commonly used to treat HAP.

Optimal treatment involves choosing the right drug or combination of drugs, the proper dose and route of administration, and the appropriate duration, 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.[26-29]

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.[30]

To improve the effectiveness of the available antibiotics specifically for HAP, 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. This antibiotic dosing logic is based on serum antibiotic concentrations in healthy

volunteers in in vitro and in vivo observations. For those reasons, it may not account fully 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.

Furthermore, measuring PK/PD only in the serum may lead to suboptimal antibiotic concentrations at the site of infection—in this case, the lung. In such cases, the antibiotic may not eradicate resistant organisms; this problem may in turn lead to treatment failure and contribute to emerging antibiotic resistance. Generally speaking, given the unique attributes of the lung that contribute to the challenge of adequately treating patients with HAP, these issues are of special concern for clinicians and others in providing fully successful services for such patients.

Categorizing antibiotics according to their PD parameters (time-dependent or concentration-dependent) is based on data relating antibiotic activity to serum drug concentrations rather than to concentrations at the site of the infection (such as the lung). Furthermore, susceptibility interpretive criteria and breakpoint determinations (MIC data) are based on established PK/PD concepts, which have been derived from serum drug concentrations. Often, dosing choices are based on assumptions that the concentration of the antibiotic at the site of infection is equal to the concentration observed in the serum.

A few studies have reported on drug penetration into the lung, generally measured as alveolar concentrations or epithelial lining fluid (ELF) concentrations. However, PD relationships and specific dosing inferences from these data have not been established. For many antibiotics, drug concentrations achieved within the lung are likely not to be equal to drug concentrations easily measured in the serum. Lodise et al. determined ELF concentrations of vancomycin in healthy patients;[31] they found that vancomycin penetrates ELF at approximately 50 percent of plasma levels, with a high level of variability among their measurements. In contrast, studies evaluating the penetration of linezolid into the lung have shown that linezolid achieves concentrations within the lung that are equal to or higher than concurrent concentrations in the serum.[32,33] Differences in chemical properties of drugs and differences in patient charachteristics such as lung inflammation also influence the penetration of drugs into the lung.[34]

Concerns in the United States and abroad about the increasing rates of superinfection 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 has decreased, especially for drugs that target Gram-negative organisms. In addition, treatment of MRSA pneumonia has become more difficult because of rising incidence of infections caused by isolates with increased minimal inhibitory concentrations (MICs) to vancomycin ("MIC creep"). To reach proposed pharmacodyamic targets, higher doses of vancomycin are needed, which increases risks of toxicities.[35] With fewer antibiotic options, ensuring the appropriate and judicious use of these drugs becomes increasingly important.[36,37]

Although optimization of antibiotic dosing is important to improve individual patient outcomes with HAP, 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/PD measures to guide dosing of antibiotics has important implications, not only for the individual patient being

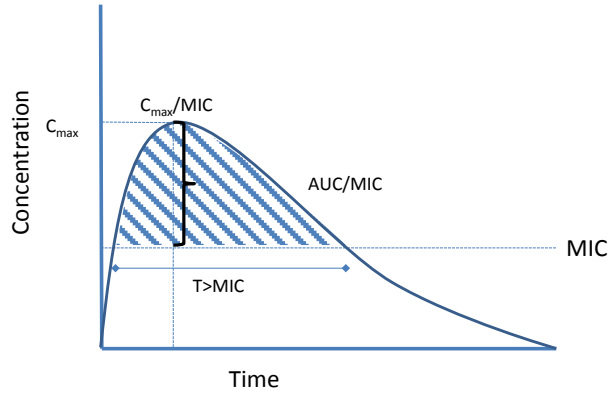
treated, but also for public health concerns. The correlation between the emergence of resistance and clinical outcomes is not fully understood, but we believe that the emergence of resistance is an important patient and societal concern. Its usefulness as a surrogate marker for clinical outcomes, however, requires further study.

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 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>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



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 HAP, correlating clinical response with specific C_{max}/MIC targets.[38,39] 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.[40-43] 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.[44] 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 MRSA 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*.[45] 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.[46] 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.[46,47]

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.[48] This observation suggested that desirable clinical results cannot reliably be achieved with empiric dosing. Current recommended dosing strategies for HAP tend to be based on animal or in vitro

models or on data from patients who are not critically ill. Today's guidance about HAP treatments typically does 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.[49] 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 HAP infections. We are not addressing community-acquired pneumonia or HAP in children or adolescents; we are also not addressing PK/PD applications for conditions other than pneumonia or organ systems other than the lungs. This focus responds to the major concerns of clinical groups that nominated the topic and the substantial challenges of successfully applying PK/PD methods to pneumonia.

As presented in thoroughly 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 HAP 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 HAP 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 PD properties of different IV antibiotics, 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. We also attempt 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 hospital-acquired pneumonia, how does using PK/PD measures to inform decisions about dosing or monitoring antibiotic treatment affect:

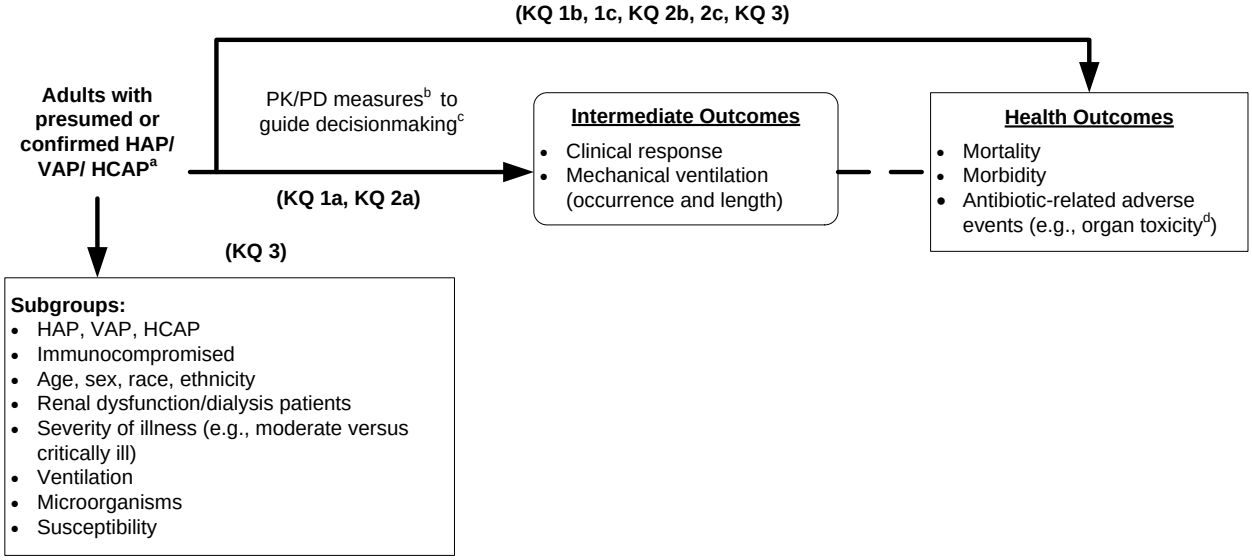
a. clinical response or mechanical ventilation?
b. morbidity or mortality?
c. rates of antibiotic-related adverse events?

Key Question 2. For people with hospital-acquired 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. For people with hospital-acquired pneumonia, 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, when examining the use of PK/PD measures to inform decisions about dosing and monitoring antibiotic treatment or when comparing prolonged or continuous infusions versus bolus infusions for beta-lactams?

Figure 2. Analytic framework for use of pharmacokinetic/pharmacodynamic (PK/PD) measures to guide antibiotic treatment for hospital-acquired 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; HAP = hospital-acquired pneumonia; HCAP = health care-associated pneumonia; KQ = Key Question; MIC = minimum inhibitory concentration; PK/PD = pharmacokinetic/pharmacodynamic; 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.[50] All methods and analyses were determined a priori.

A stakeholder panel, which was convened by the Blue Cross Blue Shield Technical Evaluation Center for the purpose of identifying relevant topics for systematic review, nominated this topic. The AHRQ Effective Health Care (EHC) program's Topic Triage group then developed and reviewed the topic; because this group deemed the topic sufficiently relevant, they moved it forward for the Topic Refinement phase. All topics are reviewed and assessed for appropriateness for systematic review (see EHC Web site for information on the process for selecting topics: http://www.effectivehealthcare.ahrq.gov/index.cfm/submit-a-suggestion-for-research/how-are-research-topics-chosen/). Once a topic is assessed and determined to be appropriate for further product development in the EHC program, AHRQ assigns it to a research team. Further development of the topic occurs with the input of Key Informants (KIs) and technical experts (see the EHC Web site for information on the research process: http://www.effectivehealthcare.ahrq.gov/index.cfm/submit-a-suggestion-for-research/what-is-the-research-process/).

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). Information provided by the topic nominator helped guide our processes; similarly, other methods and content experts and KIs provided insights to help formulate our procedures. We also conducted a scan of the relevant literature. We carried out preliminary literature searches and discussions with KIs to develop appropriate KQs.

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 email at several points: 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 comment on the data analysis plan.

Our KQs were posted for public comment on AHRQ's EHC program 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; specifically, we decided to include dose-monitoring studies, in which no therapeutic drug monitoring occurs during the studies but which apply PK/PD principles. We then drafted a protocol for the review that was posted on the same Web site. 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 through May 15, 2013; we later updated the searches through June 7, 2014. (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 TEP members 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, 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 systematic review (SR). We received no SIPs.

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 studies measure and report at least one of our specified outcomes. For both intermediate outcomes and health outcomes, randomized controlled trials (RCTs), nonrandomized controlled trials, and 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 hospital-acquired pneumonia (HAP)

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)	• Children and adolescents under 18 years of age • Fungal pneumonia • Other methods of administration (e.g., inhaled antibiotics)
Interventions	• KQ 1 and KQ 3: Use of PK/PD measures for dosing and monitoring intravenous antibiotics: o Serum concentration o Volume of distribution o Protein binding o Time above MIC o Ratio of AUC to MIC • KQ 2 and KQ 3: Prolonged or continuous infusion	• No intervention

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

Criteria	Inclusion Criteria	Exclusion Criteria
Comparators	• KQ 1 and KQ 3: o No use of PK/PD measures o Different targets of PK/PD measures o Usual care (e.g., physician discretion or judgment, local epidemiology of bacteria and resistance) • KQ 2 and KQ 3: Bolus dosing	• No comparator • Studies in which only serum concentration is measured, without targeting different serum concentration levels
Outcomes	• KQ 1a, KQ 2a, and KQ 3: Intermediate outcomes o Clinical response o Mechanical ventilation (occurrence or length) • KQ 1b, KQ 2b, and KQ 3: Health outcomes o Mortality - In hospital - Within 30 days of discharge - All-cause mortality - Mortality due to pneumonia o Morbidity - Reinfection, or two episodes of pneumonia with different pathogens - Relapse, or second episode of pneumonia with the same pathogen - Superinfection, or infection with multiple pathogens • KQ 1c, KQ 2c, and KQ 3: Antibiotic-related adverse events o Organ toxicity (e.g., hepatotoxicity, nephrotoxicity) o Hematologic effects (e.g., anemia, thrombocytopenia) o *Clostridium difficile* infection o Antibiotic resistance (reported at either the patient or the unit level)	• No outcomes of interest
Timing (length of followup)	No limits	Not applicable
Settings	• Treatment beginning in the hospital (emergency department, floor, or intensive care unit) • Treatment continuing in other settings (e.g., in the home or a skilled nursing facility)	• Treatment beginning in other settings, such as nursing homes
Admissible evidence (study design and other criteria)	• 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	• 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

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

Criteria	Inclusion Criteria	Exclusion Criteria
Time period	No date limit; searches were updated after the draft report was submitted for peer review	Not applicable

AUC = antibiotic area under the curve; HAP = hospital-acquired pneumonia; HCAP = health care–associated pneumonia; KQ = Key Question; MIC = minimum inhibitory concentration; PK/PD = pharmacokinetic/pharmacodynamic; VAP = ventilator-associated pneumonia.

We required studies to have a comparator to be included. Because of this requirement, studies lacking a comparator PK/PD target goal were not eligible; similarly, retrospective cohort studies without an appropriate comparator group were not eligible. Our goal was not to examine an individual drug's performance; rather, we focused on use of PK/PD measures to guide and optimize treatment.

Thus, many vancomycin dosing studies for *S. aureus* pneumonia using PK/PD measures would not be eligible if they did not prospectively compare two or more different dosing approaches, such as targeting two different troughs. Studies that retrospectively examined the peak or trough values that different patients *achieved* and related those data to the MIC of the organism would also not be included. Furthermore, studies evaluating extended interval aminoglycoside dosing were not included if they did not have a prospective comparator group.

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 lung infections. Because the report scope was limited to 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. Ventilator-associated tracheobronchitis (VAT) that has not become VAP would not meet the inclusion criteria for our review. PK/PD studies of VAT alone would need to be separate from VAP because the concentration of drug at the site of infection differs.

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 HAP patients. As stated in the introduction, the lung is a unique organ for drug penetration. Thus, serum concentrations for other conditions, such as sepsis, do not necessarily correlate with optimizing dosing for pneumonia.

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. For that reason, these practices do not constitute a study design for examining 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. We recorded intention-to-treat results if available.

Trained reviewers recorded 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. 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.[51] 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.[52] 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 defines 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., 2010[52]

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.[53] 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 AHRQ Task Order Officer (TOO) and an AHRQ associate editor (a senior member of another EPC) reviewed the draft report before peer review and public comment. The draft report (revised as needed) was sent to invited peer reviewers and simultaneously uploaded to the AHRQ Web site where it was available for public comment for 28 days.

We collated all reviewer comments (both invited and from the public) and addressed them individually. We documented all our responses to these comments in a disposition of comments document, which will be posted on the AHRQ EHC program 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 of the effects of using pharmacokinetic/pharmacodynamics (PK/PD) measures for dosing and other decisions for hospital-acquired pneumonia (HAP). It is then organized by Key Question (KQ) and grouped by intervention. 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

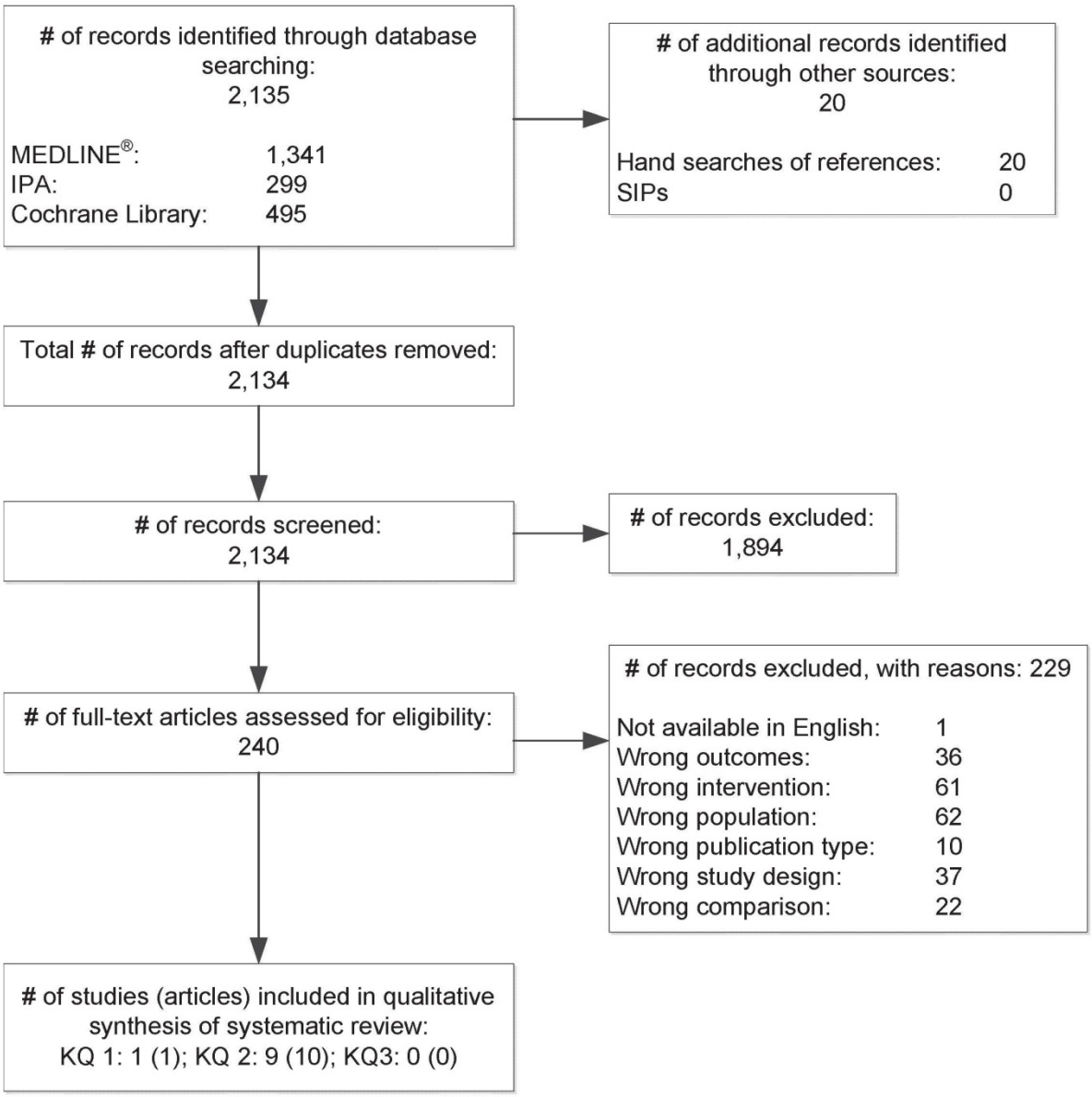
Results of our searches appear in Figure 3. From an unduplicated pool of 2,134 possible articles, we excluded 1,894 at the title and abstract review stage and another 240 at the full-text review stage.

We included 10 studies reported in 11 published articles. Of these, one study pertained to KQ 1; nine pertained to KQ 2. We identified no studies addressing KQ 3 on subgroups.

Description of Included Studies

Table 4 describes the 10 included studies (listed in alphabetical order by first author). Seven studies were randomized controlled trials (RCTs).[54-61]Two were prospective cohort studies;[62,63] one was a retrospective cohort study.[64] All seven RCTs addressed KQ 2; three were conducted by the same group of investigators in the United States, and the other four were conducted in the United States, Thailand, Germany and China. One prospective cohort study for KQ 2 was conducted in Italy and the other in India. The retrospective cohort study for KQ 1 was performed in Spain. Five RCTs were funded by the pharmaceutical industry; one trial and two cohort studies were supported by government or an academic institution; and two studies, one trial and one cohort, reported no source of support. We rated five of the trials and one cohort study as medium risk of bias and two trials and two cohort studies as high risk of bias.

Figure 3. Disposition of articles about using PK/PD measures in hospital-acquired pneumonia



IPA = International Pharmaceutical Abstracts; KQ = Key Question; PK/PD = pharmacokinetic/pharmacodynamic; SIP = Scientific Information Packet

Table 4. Characteristics of included studies

Author, Year Design Country Setting	Population N Study Duration Funding	Mean Age (SD), Percentage Female Percentage Non-White	Intervention, n Comparator, n	Baseline APACHE[65] II Score, Mean (SD)	Risk of Bias
Fahimi et al., 2012[63] Prospective cohort India ICU	Ventilator-acquired pneumonia (HAP and HCAP patients excluded) 61 Unclear NR	53.81 (21.77) 50.8% NR	Continuous infusion: 31 Intermittent infusion: 30	Continuous infusion: 18.87 (5.95) Intermittent infusion: 20.43 (6.17) p=0.319	Medium
Hanes et al., 2000[59] RCT United States ICU	Nosocomial pneumonia 31 NR (based on each patient's clinical response)	NR for total 19% NR	Continuous infusion: 17 Intermittent infusion: 14	Continuous infusion: 12.8 (4.6) Intermittent infusion: 10.9 (5.8)	Medium
Jaruratanasirikul et al., 2012 [60] RCT Thailand ICU	Ventilator-acquired pneumonia 11 3 days Academic	50 (16) 10% NR	Continuous infusion: NR Intermittent infusion: NR	Continuous infusion: NR Intermittent infusion: NR	High
Lorente et al., 2009[64] 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[57] McNabb et al., 2001[55] RCT United States ICU	Hospital-acquired pneumonia 41 (6 non-evaluable because duration of therapy was < 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[54] RCT United States ICU	Hospital-acquired 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[58] RCT United States ICU	Hospital-acquired pneumonia 34 NR Pharmaceutical	47 (18) 35% NR	Continuous infusion: 17 Intermittent infusion: 17	Continuous infusion: 15 (4) Intermittent infusion: 14 (4)	Medium

Table 4. Characteristics of included studies (continued)

Author, Year Design Country Setting	Population N Study Duration Funding	Mean Age (SD), Percentage Female Percentage Non-White	Intervention, n Comparator, n	Baseline APACHE[65] II Score, Mean (SD)	Risk of Bias
Sakka et al., 2007[56] 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[62] Prospective cohort Italy Hospital	Hospital-acquired 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
Wang, 2009[61] RCT China ICU	Hospital-acquired pneumonia 30	NR for total 11 (36.7) NR	Continuous infusion: 15 Intermittent infusion: 15	Continuous infusion: 20.33 (4.29) Intermittent infusion: 17.33 (5.82)	Medium

APACHE = Acute Physiology and Chronic Health Evaluation scale; ICU = intensive care unit; MIC = minimum inhibitory concentration; n = number; 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. Specifically, the study defined "cure" as no further specimens obtained for microbiologic testing, and the mortality outcome included both death and patients who left the hospital against medical advice.[62] Evidence is insufficient to draw conclusions about the effect of using 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.[62] 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. We assessed this study as 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). Of the 205 patients in the group with both PK/PD measures, 81 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.

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, n (%)
Scaglione et al., 2009[62]	G1: Serum concentration + MIC: 205 G2: Serum concentration or MIC or no PK/PD measures: 433 (number ventilated: 52)	Definition: absence or improvement of clinically significant symptoms and signs such that no additional therapy was required G1: 168 (82[a]) G2: 293 (68[a]) p=NR	Definition: persistence or progression of symptoms and signs or death of the patient G1: 37 (18) G2: 140 (32) p<0.001	Definition: not defined G1: 4.28 (1.3) G2: 5.39 (1.8) p=0.09	Definition: mortality or patients left hospital against medical advice G1: 21 (10) G2: 102 (24) p<0.001

G = group; MIC = minimum inhibitory concentration; n = number; NR = not reported; PK/PD = pharmacokinetic/pharmacodynamic; SD = standard deviation.
[a]Calculated by systematic review authors.

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.

Antibiotic-Related Adverse Events

This prospective cohort study did not address organ toxicity, hematological effects, *Clostridium difficile (C. difficile)* infection, or antibiotic resistance. The investigators stated that all treatments were well tolerated and that study groups did not differ on these outcomes.

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).[62]

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	Precise	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	Precise	Insufficient

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 two small trials.[55,57,59] and one prospective cohort.[63]

Evidence is insufficient to draw conclusions about the effect of continuous infusions versus intermittent infusions on the rates of antibiotic-related adverse events.[54-58,60,64]

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 nine studies (10 articles).[54-61,63,64] All nine studies included patients with HAP in the intensive care unit (ICU) setting. Seven were RCTs;[54-61] one was an historical cohort study,[64] and one a prospective cohort.[63] Characteristics of the patients in these studies are shown in Table 7.

Table 7. Severity of illness and other population characteristics

Author, Year	Intervention, n Comparator, n	Baseline APACHE II Score, Mean (SD)	Other Severity of Illness Measures	Other Relevant Baseline Characteristics
Fahimi et al., 2012[63]	Continuous infusion: 31 Intermittent infusion: 30	Continuous infusion: 18.87 (5.95) Intermittent infusion: 20.43 (6.17) p=0.319	NR	Cardiac and vascular disorders, n (%) G1: 10 (32.3) G1: 9 (30) p=0.85 Pulmonary disorders, n (%) G1: 17 (56.7) G2: 18 (58.1) p=0.91

Table 7. Severity of illness and other population characteristics (continued)

Author, Year	Intervention, n Comparator, n	Baseline APACHE II Score, Mean (SD)	Other Severity of Illness Measures	Other Relevant Baseline Characteristics
Hanes et al., 2000[59]	Continuous infusion: 17 Intermittent infusion: 14	Continuous infusion: 12.8 (4.6) Intermittent infusion: 10.9 (5.8)	NR	Mean CLCr, mL/min (SD) G1: 96.8 (23.3) G2: 96.8 (21.6) p=NS
Jaruratanasirikul et al., 2012 [60] Jaruratanasirikul et al., 2012 [60]	Continuous infusion: NR Intermittent infusion: NR	Continuous infusion: NR Intermittent infusion: NR	NR	NR
Lorente et al., 2009[64]	Continuous infusion: 37 Intermittent infusion: 46	Continuous infusion: 16.1 (2.09) Intermittent infusion: 16.2 (2.15)	NR	COPD, n Overall: NR G1: 5 G2: 5 p= 0.75 Mean CLCr, mL/min (SD) Overall: NR G1: 102.2 (14.54) G2: 101.3 (11.80) p=0.75 SOFA score at suspicion of VAP, mean (SD) G1: 9.1 (2.23) G2: 8.8 (2.06) p=0.57 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

Table 7. Severity of illness and other population characteristics (continued)

Author, Year	Intervention, n Comparator, n	Baseline APACHE II Score, Mean (SD)	Other Severity of Illness Measures	Other Relevant Baseline Characteristics
Nicolau et al., 2001[57] McNabb et al., 2001[55]	Continuous infusion: 18 Intermittent infusion: 17	Continuous infusion: 15.5 (6.3) Intermittent infusion: 13.9 (4.4)	NR	Ventilated at baseline, n G1: 16 G2: 16 p= 0.581 Comorbidites, n (%) COPD G1: 1 (6) G2:0 (0), p=NR CVD G1: 9 (50) G2: 5 (29), p=NR Alcoholism G1: 6 (33) G2: 4 (24), p=NR Diabetes mellitus G1: 3 (17) G2: 2 (12), p=NR Cancer G1: 2 (11) G2: 1 (6), p=NR

Table 7. Severity of illness and other population characteristics (continued)

Author, Year	Intervention, n Comparator, n	Baseline APACHE II Score, Mean (SD)	Other Severity of Illness Measures	Other Relevant Baseline Characteristics
Nicolau et al., 2001[57] McNabb et al., 2001[55] (continued)				Systolic BP ≤90, mm Hg G1: 2 (11) G2: 2 (12), p=NR Serum creatinine ≥1.7, mg/dL G1: 0 (0) G2: 1 (6), p=NR Immunosuppression (steroids) G1: 4 (22) G2: 4 (24) History of smoking G1: 4 (22) G2: 2 (12), p=NR
Nicolau et al., 1999[54]	Continuous infusion: 13 Intermittent infusion: 11	Continuous infusion: 14.5 (4.7) Intermittent infusion: 13.8 (5.0)	NR	Days from admission to initiation of therapy, median (range) Overall: NR G1: 8 (4-20) G2: 7 (3-26) p=NR Creatinine clearance, mean (SD) Overall: NR G1: 100 (38) G2: 104 (32) p=NR
Nicolau et al., 1999[58]	Continuous infusion: 17 Intermittent infusion: 17	Continuous infusion: 15 (4) Intermittent infusion: 14 (4)	NR	Estimated creatinine clearance, mean (SD) G1: 92 (38) G2: 102 (30) p=NR
Sakka et al., 2007[56]	Continuous infusion: 10 Intermittent infusion: 10	Continuous infusion: 26 (6) Intermittent infusion: 28 (5)	SOFA score ± SD (range) Overall: NR G1: 7 ± 2 (4-10) G2: 6 ± 3 (1-10) SAPS II score ± SD (range) G1: 44 ± 14 (28-77 G2: 43 ± 12 (22-62)	Height, cm (SD) G1: 171 (8) G2: 170 (7) p=NR Weight, kg (SD) G1: 73 (8) G2: 78 (14) p=NR BSA, m2 (SD) G1: 1.84 (0.14) G2: 1.89 (0.16) p=NR Creatinine clearance, ml/min (SD) G1: 122 (33) G2: 128 (35) p=NR

Table 7. Severity of illness and other population characteristics (continued)

Author, Year	Intervention, n Comparator, n	Baseline APACHE II Score, Mean (SD)	Other Severity of Illness Measures	Other Relevant Baseline Characteristics
Wang, 2009[61]	Continuous infusion: 15 Intermittent infusion: 15	Continuous infusion: 20.33 (4.29) Intermittent infusion: 17.33 (5.82)	NR	NR

APACHE = Acute Physiology and Chronic Health Evaluation scale; BP = blood pressure; BSA = body surface area; CrCl = creatinine clearance; cm = centimeter; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; dL = decaliter; G = group; Hg = mercury; kg = kilogram; mg = milligram; min = minute; ml = milliliters; mm = millimeters; n = number; NR = not reported; SAPS = Simplified Acute Physiology Score; SD = standard deviation; SOFA = Sepsis-related Organ Failure Assessment; VAP = ventilator-acquired pneumonia.

Of the nine studies in our KQ 2 analysis, four medium risk of bias studies (three trials, one prospective cohort) evaluated the effect of continuous versus intermittent administration of beta-lactam antibiotics on intermediate clinical outcomes, duration of mechanical ventilation, and superinfection.[55,57,59-61,63]

Four RCTs (two medium risk of bias and two high risk of bias) reported rates of antibiotic-related adverse events.[54,56,58,60]

We excluded one study (high risk of bias) from the analysis of intermediate outcomes and morbidity or mortality because it was retrospective.[64] We included it for the analysis of rates of adverse events.

Of the three studies rated high risk of bias, one study received this rating because of high risk of selection bias and confounding.[64] The second study received this rating because of high risk of selection bias, measurement bias, and confounding.[56] The third study had a very small number of patients, a high risk of selection bias, and confounding.[60] Appendix B presents detailed information on risk-of-bias ratings.

Intermediate and Health Outcomes

Three RCTs and one prospective cohort study met our criteria for assessment of intermediate and health outcomes (Table 8). One open-label RCT reported clinical response, length of mechanical ventilation, and superinfection.[55,57] The investigators excluded immunocompromised patients such as those with AIDS and neutropenia. Clinical cure was defined 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.[55,57]

Another RCT, also using ceftazidime, defined success as complete resolution of all signs and symptoms of pneumonia and improvement or in lack of progression of all abnormalities on the chest radiograph.[59] Patients with creatinine clearances of <30 mL/min or bacterial pathogens resistant to ceftazidime were excluded. The percentage of patients achieving success was higher in the intermittent infusion group than in the continuous infusion group, but the difference was not statistically significant (56% versus 71%, $p = 0.63$).

Two trials, one randomized[61] and the other nonrandomized,[63] used the Clinical Pulmonary Infection Score (CPIS) as their marker of success. In the randomized trial, all patients were infected with *A. baumannii* and treated with meropenem. Success was a CPIS of <6; the authors presented mean scores, with no statistical testing for differences, for days 3, 5, and 7. All patients achieved a CPIS of <6 by day 7.[61] In the nonrandomized trial, investigators excluded immunocompromised patients (i.e., AIDS, neutropenia) and those with early-onset HAP or HCAP without any risk factors for multidrug-resistant pathogens.[63] The investigators evaluated the use of piperacillin/tazobactam by either intermittent infusion or prolonged infusion for the treatment of VAP. The two groups did not differ significantly in CPIS scores on days 1, 3 or 8; mean CPIS scores in each group rose at each measurement day, ending with 8.51 (intermittent) versus 8.60 (prolonged) on day 8.

We excluded one study from the analysis of intermediate and health outcomes because of its retrospective design.[64]

Table 8. Intermediate and health outcomes for studies addressing Key Question 2

Author, Year	Intervention, n Comparator, n	Clinical Response, n (%)	Duration of Mechanical Ventilation, Days (SD)	Superinfection, n (%)
Fahimi et al., 2012[63]	Continuous infusion: 31 Intermittent infusion: 30	Clinical pulmonary infection score Day 1 G1: 7.12 (1.33) G2: 6.96 (1.77) p=0.687 Day 3 G1: 8.74 (1.76) G2: 8.66 (2.48) p=0.892 Day 8 G1: 8.51 (2.07) G2: 8.60 (2.22) p=0.880	Definition: duration of mechanical ventilation days G1: 42.61 (29.10) G2: 37.96 (28.23) p=0.529	NR
Hanes et al., 2000[59]	Continuous infusion: 17 (I excluded from outcome analysis) Intermittent infusion: 14	Cure Definition: complete resolution of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on the chest radiograph: G1: NR (56) G2: NR (71) p=0.63	Definition: duration of mechanical ventilation days G1: 22.9 (19.9) G2: 13.3 (6.1) p=0.16	Definition: pneumonia superinfection (most commonly caused by *A calcoaceticus*) G1: NR (44) G2: NR (2) p=NR Within treatment failures G1: NR (71) G2: NR (75) p=NR

Table 8. Intermediate and health outcomes for studies addressing Key Question 2 (continued)

Author, Year	Intervention, n Comparator, n	Clinical Response, n (%)	Duration of Mechanical Ventilation, Days (SD)	Superinfection, n (%)
Nicolau et al., 2001[57] McNabb et al., 2001[55]	G1: Continuous infusion: 17 G2: Intermittent infusion: 18	Cure Definition: complete resolution of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on the chest radiograph: G1: 7 (41) G2: 6 (33) Improvement Definition: improvement of signs and symptoms of pneumonia, with evidence of infection remaining G1: 9 (53) G2: 9 (50) Failure Definition: persistence or progression of signs and symptoms of pneumonia, development of new pulmonary or extrapulmonary clinical findings consistent with active infection, progression of radiographic abnormalities, or death due to infection G1: 1 (6) G2: 3 (17) p=0.592 for all three measures	Definition: duration of mechanical ventilation during enrollment G1: 7.9 (4.0) G2: 8.3 (4.3) p=0.970	Definition: superinfection with MRSA G1: 0 (0) G2: 1 (5.6) p=NR
Wang, 2009[61]	Continuous infusion: 15 Intermittent infusion: 15	Success Definition: CPIS <6 Day 3 Continuous infusion: 5 (33.33) Intermittent infusion: 6 (40) Day 5 Continuous infusion: 14 (93.33) Intermittent infusion: 13 (86.67) Day 7 Continuous infusion: 15 (100) Intermittent infusion: 15 (100)	NR	NR

G = group; MRSA = methicillin-resistant *S. aureus*= staphylococcus aureus*;* n = number; NR = not reported; SD = standard deviation.

Duration of mechanical ventilation also did not differ significantly between the groups in the three trials.[55,57,59,63] One trial presented data on relapse and mortality; on both measures, differences between groups were not statistically significant.[61]

No investigators reported on rates of reinfection; two trials reported on rates of superinfection.[55,57,59] In one trial, methicillin-resistant *Staphylococcus aureus* (MRSA) occurred in one patient in the intermittent infusion group and in no patient in the continuous infusion group.[55,57] The other trial reported high rates of superinfection, most commonly with *A. calcoaceticus*. Pneumonia caused by *Acinetobacter calcoaceticus* occurred in 44 percent of their continuous infusion group and 22 percent of the intermittent infusion group.[59] For patients with

treatment failures, 71 percent of the continuous infusion group and 75 percent of the intermittent infusion group developed superinfections.[59] Neither study presented any results for tests of statistical significance for these data.

Antibiotic-Related Adverse Events

Six studies (four RCTs; one retrospective and one prospective cohort study) reported information on rates of antibiotic-related adverse events (Table 9). Four studies reported no adverse events attributed to the treatment regimens.[54,56,58,60] 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.[55,57] 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.[55,57] No study reported on hematological adverse effects.

One RCT and the retrospective cohort study reported rates of resistance or development of resistance during the study periods.[55,57,64] The trial prospectively evaluated data (333 serial MICs) for the identified isolates, but the investigators reported that they did not observe any development of resistance during the study period in either group.[55,57] The cohort study researchers reported that they observed no antibiotic resistance during the treatment course in either group.[64]

Table 9. Antibiotic-related adverse event outcomes for studies addressing Key Question 2

Author, Year	Intervention, n Comparator, n	Outcome	Results, n (%)
Jaruratanasirikul et al., 2012 [60]	G1: Continuous infusion: NR G2: Intermittent infusion: NR	Adverse events attributed to dosing regimen of doripenem	G1: Continuous infusion: n= NR, authors stated well tolerated and no reported adverse events G2: Intermittent infusion: n= NR, authors stated well tolerated and no reported adverse events
Lorente et al., 2009[64]	G1: Continuous infusion: 37 G2: Intermittent infusion: 46	Antibiotic resistance	G1: 0 (0) G2: 0 (0) p=NR
Nicolau et al., 2001[57] McNabb et al., 2001[55]	G1: Continuous infusion: 18 G2. Intermittent infusion: 17	Antibiotic resistance	G1: 0 (0) G2: 0 (0) p=NR
		C. difficile 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

Table 9. Antibiotic-related adverse event outcomes for studies addressing Key Question 2 (continued)

Author, Year	Intervention, n Comparator, n	Outcome	Results, n (%)
Nicolau et al., 1999[54]	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[58]	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[56]	G1: Continuous infusion: 10 G2: Intermittent infusion: 10	Imipenem-related adverse reactions (e.g., seizures)	G1: 0 (0) G2: 0 (0)

G = group; n = number; NR = not reported.

Table 10 presents the characteristics of the organisms identified for the studies included for KQ 2. The majority of the organisms identified were Gram-negative. Four studies reported on susceptibility data for the organisms isolated.[56,57,61,63] Two studies used these MIC data to evaluate pharmacodynamic profiles of the regimens given.[56,57]

Table 10. Organism characteristics for studies addressing Key Question 2

Author, Year	Intervention, n Comparator, n	Microorganism Responsible for Pneumonia, n (%)	Organism MICs	Gram-Negative vs. Gram-Positive
Fahimi et al., 2012[63]	Continuous infusion: 31 Intermittent infusion: 30	*Acinetobacter baumannii* G1: 9 (29.0) G2: 5 (16.7) *Enterobacter* spp. G1: 2 (6.5) G2: 2 (6.7) *Escherichia coli* G1: 3 (9.7) G2: 2 (6.7) *Klebsiella pneumoniae* G1: 5 (16.1) G2: 4 (13.1) *Pseudomonas aeruginosa* G1: 5 (16.1) G2: 6 (20.0)	NR	NR

Table 10. Organism characteristics for studies addressing Key Question 2 (continued)

Author, Year	Intervention, n Comparator, n	Microorganism Responsible for Pneumonia, n (%)	Organism MICs	Gram-Negative vs. Gram-Positive
Lorente et al., 2009[64]	Continuous infusion G1: 37 Intermittent infusion G2: 46	*Acinetobacter baumannii* G1: 2 (5.4) G2: 2 (4.3) *Citrobacter* spp. G1: 1 (2.7) G2: 2 (4.3) *Enterobacter* spp. G1: 4 (10.8) G2: 5 (10.9) *Escherichia coli* G1: 5 (13.5) G2: 8 (17.4) *Haemophilus influenzae* G1: 4 (10.8) G2: 4 (8.7) *Klebsiella pneumoniae* G1: 2 (5.4) G2: 2 (4.3) *Morganella morganii* G1: 3 (8.1) G2: 3 (6.5) *Proteus mirabilis* G1: 1 (2.7) G2: 2 (4.3) *Pseudomonas aeruginosa* G1: 11 (29.7) G2: 13 (28.3) *Serratia marcescens* G1: 4 (10.8) G2: 5 (10.9) All p = 0.99	NR	All identified organisms were Gram-negative

Table 10. Organism characteristics for studies addressing Key Question 2 (continued)

Author, Year	Intervention, n Comparator, n	Microorganism Responsible for Pneumonia, n (%)	Organism MICs	Gram-Negative vs. Gram-Positive
Nicolau et al., 2001[57] McNabb et al., 2001[55]	Continuous infusion G1: 18 Intermittent infusion G2: 17	*Acinetobacter baumanii* G1: 0 G2: 2 (6) *Enterobacter* spp. G1: 2 (10) G2: 3 (10) *Escherichia coli* G1: 1 (5) G2: 2 (6) *Haemophilus influenzae* G1: 4 (20) G2: 6 (19) *Klebsiella pneumoniae* G1: 1 (5) G2: 5 (16) *Proteus mirabilis* G1: 1 (5) G2: 3 (10) *Pseudomonas aeruginosa* G1: 6 (30) G2: 3 (10) Methicillin sensitive *Staphylococcus aureus* (MSSA) G1: 3 (15) G2: 4 (13) Other G1: 2 (10) G2: 3 (10)	NR	Gram-negative organisms accounted for more than 90% of the isolated species. With the exception of MSSA (3 cases in G1 and 4 cases in G2), gram-negative organisms accounted for all identified species listed.
Nicolau et al., 1999[54]	Continuous infusion: 13 Intermittent infusion: 11	NR	NR	NR
Nicolau et al., 1999[58]	Continuous infusion: 17 Intermittent infusion: 17	46 pathogens were isolated in this study population; the most common organisms isolated were *Haemophilus influenzae, Pseudomonas aeruginosa, Klebsiella pneumonia,* and Methicillin-susceptible *Staphylococcus aureus* (MSSA)	Ceftazidime MIC (mg/L) (Broth dilution technique): n (%) MIC of 8: 4 (9) MIC of 4: 6 (13) MIC of 2: 5(11) MIC of 0.5-1 8: (17) MIC ≤0.25: 23 (50)	With the exception of MSSA, three of the four named pathogens isolated were Gram-negative organisms.

Table 10. Organism characteristics for studies addressing Key Question 2 (continued)

Author, Year	Intervention, n Comparator, n	Microorganism Responsible for Pneumonia, n (%)	Organism MICs	Gram-Negative vs. Gram-Positive
Sakka et al., 2007[56]	Continuous infusion: 10 Intermittent infusion: 10	*Acinetobacter baumannii* G1: 0 G2: 1 *Acinetobacter lwoffii* G1: 1 G2: 0 *Enterobacter cloacae* G1: 2 G2: 1 *Enterobacter gergoviae* G1: 1 G2: 0 *Escherichia coli* G1: 1 G2: 2 *Klebsiella pneumoniae* G1: 2 G2: 3 *Pseudomonas aeruginosa* G1: 3 G2: 1 *Proteus mirabilis* G1: 0 G2: 1 *Serratia marcescens* G1: 0 G2: 1	MIC ≤ 0.125 mg/liter G1: 5 G2: 6 MIC of 0.25 G1: 1 G2: 3 MIC of 0.5 G1: 1 G2: 1 MIC of 2 G1: 1 G2: 0 MIC of 1 G1: 2 G2: 0	All identified organisms were Gram-negative.
Wang, 2009[61]	Continuous infusion: 15 Intermittent infusion: 15	*Acinetobacter baumannii* G1: 15 G2: 15	NR	*Acinetobacter baumanni* is Gram-negative

G = group; mg/L = milligrams per liter; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant staphylococcus aureus, n = number; NR = not reported; spp = species.

In one Nicolau et al. study, the continuous infusion regimen of ceftazidime produced drug serum concentrations that exceeded the MIC breakpoint of 8 mg/L for *Pseudomonas aeruginosa* for 100 percent of the dosing interval for all patients in the continuous infusion group.[58] This means that serum antibiotic concentrations were sufficient to inhibit the growth of ceftazidime-susceptible *Pseudomonas aeruginosa* for 100 percent of the dosing interval. For patients in the intermittent infusion group, the MIC was exceeded for 100 percent of the dosing interval for organisms with an MIC $\leq$2 mg/L, an average of 92 percent of the dosing interval for organisms with an MIC $\leq$4 mg/L, and an average of 82 percent of the dosing interval for organisms with an MIC of 8 mg/L. So, for more susceptible organisms (those with lower MICs), intermittent infusion of ceftazidime provided antibiotic concentrations sufficient to inhibit bacterial growth for more time during the dosing interval than for less susceptible organisms (those with higher MICs).

The Sakka et al. study showed that the intermittent infusion of imipenem (1 g every 8 hours) achieved a probability of target attainment of 88 percent for organisms with an MIC of 2 mg/L, using a target of drug concentration exceeding the MIC for 40 percent of the dosing interval.[56] So, for organisms with MIC values of 2 mg/L or less, the intermittent infusion of imipenem had a 88 percent probability of reaching the predefined PD target for drug concentrations sufficient to

inhibit bacterial growth for 40 percent of the dosing intervial. The probability of target attainment decreased for organisms with MICs >2 mg/L (less susceptible organisms). In the continuous infusion group, the probability of target attainment was 90 percent for organisms with an MIC of 2 mg/L and 86 percent for organisms with an MIC of 4 mg/L, using the target of 40 percent (drug concentration exceeding the MIC for 40 percent of the dosing interval).

Neither the Nicolau et al. nor the Sakka et al. studies related results of the pharmacodynamics analyses to patient outcomes.

One RCT and one retrospective cohort study reported on rates of resistance or development of resistance during the study periods.[55,57,64] The trial prospectively evaluated susceptibility data (333 serial MICs) for the identified isolates,[55,57] 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.[64]

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 (Table 11). The main reason was the small number of studies with small numbers of patients, which generally resulted in unknown consistency and imprecision. In addition, aggregate risk of bias was medium or high for all outcomes for which we had any evidence.

Key Question 3. Subgroup Analyses

We found no studies meeting inclusion criteria that answered any questions about the impact of using PK/PD measures or principles on either 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 11. 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	3 RCTs (n=96)	Medium	Consistent	Direct	Imprecise	Insufficient
		1 prospective cohort (n=61)	Medium	NA	Direct	Imprecise	
	Mechanical ventilation	2 RCTs (n=66)	Medium	Consistent	Direct	Imprecise	Insufficient
		1 prospective cohort (n=61)	Medium	NA	Direct	Imprecise	
	Treatment failure	1 RCT (n=35)	Medium	NA	Direct	Imprecise	Insufficient
Morbidity and mortality outcomes	Superinfection	2 RCTs (n=66)	Medium	Inconsistent	Indirect	Imprecise	Insufficient
Antibiotic-related adverse events	Organ toxicity	1 RCT (n=35)	Medium	NA	Indirect	Imprecise	Insufficient
	Hematologic effects	0 (0)	NA	NA	NA	NA	NA
	C. difficile infection	1 RCT (n=35)	Medium	NA	Direct	Imprecise	Insufficient
	Antibiotic resistance	1 RCT (n=35)	Medium	NA	Direct	Imprecise	Insufficient
		1 retrospective cohort (n=83)	High	NA	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
	Adverse events attributed to the dosing regimen of doripenem	1 RCT (n=NR)	High	NA	Unknown	Imprecise	Insufficient
	Infusion-related adverse effects (e.g., phlebitis)	1 RCT (n=34)	Medium	NA	Unknown	Imprecise	Insufficient

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

Comparative evidence is scarce on use of pharmacokinetic/pharmacodynamic (PK/PD) measures in dosing or monitoring. Similarly, little evidence is available on use of PK/PD strategies in adult patients with HAP who are being treated with intravenous (IV) antibiotics.

The strength of evidence is insufficient to conclude whether using measures to inform decisions about dosing or monitoring IV antibiotic treatment (Key Question [KQ] 1) improves either intermediate or health outcomes. We found only a single prospective cohort study (which we 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). Pertinent studies found no significant differences 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

In screening titles and abstracts identified by our searches, we determined that very little research has focused on the use of PK/PD measures in dosing or monitoring adult patients with hospital-acquired pneumonia (HAP) (including ventilator-associated pneumonia [VAP] and health-care-associated pneumonia [HCAP]) being treated with IV antibiotics. This dearth of studies suggests that the research conducted to date has been conducted in in vitro and animal studies. In what little is published 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, HAP) without reporting outcomes for patients with HAP 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.[49] Of the seven studies 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 their small sample sizes and retrospective design. Moreover, they were not focused on using PK/PD measures to adjust 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 (published in 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.[59] Recently, Mohd Hafiz and colleagues 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 included inconsistent antibiotic doses and endpoints, heterogeneous patient groups, and small sample sizes.[66]

Emerging microbial resistance concerns motivate clinicians and policymakers alike. These changes have led to efforts to develop more effective strategies for using current therapies. For example, the Agency for Healthcare Research and Quality (AHRQ) has made investments in patient safety, with specific attention to health care-associated infections and antibiotic resistance. In addition, the National Institutes of Health has issued new funding opportunities to encourage development of new antibiotics.

Many national and international organizations have recognized the growing global problem of antibiotic resistance and have made efforts to raise public awareness and coordinate actions to address problems related to resistance. For example, the Centers for Disease Control and Prevention has launched the Get Smart Campaign to encourage the judicious use of antibiotics. Strategies often employed include infection control and prevention techniques such as hand-washing, development of rapid, point-of-care diagnostic tests to diagnose infection more rapidly and accurately, public policies to support development and approval of new drugs to treat resistant infections, and implementation of coordinated efforts to optimize antibiotic use through practices referred to as antibiotic stewardship.

Antibiotic stewardship programs have several goals. Among them are improving appropriate use of antibiotics by promoting antibiotic use only when indicated and selection of optimal antimicrobial drug regimens to improve clinical outcomes. Minimizing toxicity and other adverse events, including limiting the emergence of antibiotic-resistant strains of bacteria, are related goals. Such programs often focus on streamlining antimicrobial therapy, de-escalating or targeting antibiotics based on microbiological data, minimizing excessive durations of antibiotic courses, and optimizing antibiotic doses.

The Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America, and the Pediatric Infectious Diseases Society have all made recommendations to the Centers for Medicare & Medicaid Services to require antibiotic stewardship programs in all acute care hospitals in the United States.[67] Pharmacodynamic dose optimization has been suggested as a strategy that antibiotic stewardship programs can employ to improve antibiotic use.[68] In fact, the IDSA guidelines for developing an institutional program to enhance antimicrobial stewardship refer to PK and PD considerations as important parts of antimicrobial stewardship.[69]

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 (populations, interventions, comparators, outcomes, timing, settings) structure. Studies instead evaluated heterogeneous treatment effects and diverse patient populations.

Implications for Clinical and Policy Decisionmaking

Given the dearth of findings in this review, the evidence base provides little guidance for either clinical or policy decisionmaking. We comment here on two key issues that warrant attention by health professionals, policymakers, and society at large; we offer specific recommendations about filling these research gaps below.

First, as antimicrobial resistance becomes a global problem, appropriate use of antibiotics is of paramount importance. Appropriate use encompasses optimal dosing strategies that are cost-effective, can improve patient outcomes, and can combat further development of resistance. These matters are relevant to clinicians, hospital administrators, insurers, patients, and public-sector agencies. With respect specifically to PK/PD approaches, of particular interest are exposure-response relationships of antibiotics, antibiotic use in "real-world" clinical settings (all types of hospitals and intensive care units [ICUs]), and a broad range of patient-centered outcomes (clinical response, morbidity, mortality, and adverse events) as well as costs of care.

Second, almost a decade ago, the American Thoracic Society (ATS) redefined its dosing guidelines based on PK/PD principles and clinical trial efficacy data.[1] Nevertheless, the effectiveness of the dosing strategies described in these guidelines remains unclear. Clinicians and policymakers alike would benefit from updated information that will point to more effective strategies for using current therapies that are now widely available.

In summary, despite the theoretical advantages of optimizing IV antibiotic dosing using PK/PD principles in patients with HAP, 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 Systematic Review Process

This review focused on the comparative effectiveness of using PK/PD measures to monitor and adjust dosing of IV antibiotics for HAP in comparison with no care, usual care, or different targets of PK/PD measures. Because our focus was only HAP (including VAP and HCAP), we omitted any study that included community-acquired pneumonia or involved 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. Also, our focus was on patient-oriented and clinical outcomes.

We did not address cost outcomes in this review. While screening studies for inclusion, we did observe some drug comparison studies reporting on the cost-effectiveness of IV antibiotics in HAP, but these studies did not meet the eligibility criteria for this systematic review. No studies directly reported on the cost-effectiveness of using PK/PD measures in dosing or monitoring IV antibiotics in treating patients with HAP. One study included in this review, comparing continuous infusion with intermittent infusion of ceftazidime in ICU patients with HAP, found continuous infusions were significantly lower in cost than intermittent infusion.[55]

Evidence-based Practice Center (EPC) reviewers consider the applicability of the evidence to key populations, major outcomes, and the like, to help stakeholders determine the applicability of the evidence to their own circumstances. As discussed above, the lack of studies precluded any in depth discussion in regard to applicability of this evidence base.

Limitations of the Evidence Base

Our review highlights the considerable limitations of the available evidence. Despite our efforts to cast a wide net for usable studies, only six studies met criteria for inclusion. Our review addressed the use of PK/PD measures or strategies to dose and monitor IV antibiotics in treating patients with HAP. Therefore, our focus was on the lung, a unique organ for drug penetration.

Serum concentrations for other conditions, such as sepsis, do not necessarily correlate with optimizing dosing for pneumonia, and thus we did not include such studies in this review.

Systematic review methods require rating the risk of bias of all included studies; applying internationally accepted methods to do this led to ratings of "high" risk of bias for half of the six studies that we could include. We opted to retain these three studies in our evidence base. Although EPCs that adopt a "best evidence" approach for certain clinical topics with large numbers of trials or observational studies might have excluded high risk-of-bias studies from their main analyses, doing so here would have reduced the evidence base to even lower levels (e.g., three studies for KQ 2) and eliminated even suggestive information from consideration.

Review procedures also require grading strength of the bodies of evidence. Again, following accepted EPC procedures, we determined that evidence was uniformly insufficient to allow any conclusions to be drawn about the two main KQs. The main problems were small numbers of patients, lack of reporting of clinical or patient-centered outcomes, 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.

We did exclude several studies from our analysis because of mixed patient populations, lack of an intervention group, or inadequate clinical outcome reporting. The limitations of such studies stemmed from several problems. First, although many studies involved patients with HAP, the overall study population in these investigations tended to be mixed. Typically, analysts did not report findings specifically for patients with HAP. For example, studies comparing continuous with intermittent infusions of beta-lactams (KQ 2) often do not focus solely on subjects with HAP; neither do they present 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. Some do not address clinical outcomes at all. 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 limitations in these studies restricted our review. In general, the trials were small and not powered to demonstrate any significant differences between groups. As noted above, we rated three studies as high risk of bias (three medium risk of bias and none low risk of bias). The two main problems were high risk of selection bias and confounding (i.e., researchers did not rule out any impact from a concurrent intervention or an unintended exposure).

Research Gaps

Review procedures call for identifying specific and important gaps in the evidence base. We offer here some specific suggestions for improving future investigations, considering both study design and conduct as well as choice of topics for research.

First, whether use of PK/PD measures for informing dosing decisions for patients with HAP influences clinical outcomes remains unknown, largely because of both the absence of studies and 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, two key topics were not addressed in most investigations: (1) use of targeted and monitored antibiotic concentrations to tailor antibiotic doses of individual patients and (2) 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, especially disease or death. In this review, only one RCT evaluated clinical outcomes for patients with HAP receiving continuous versus intermittent ceftazidime infusions.[57]

Third, the effect of optimizing antibiotic dosing based on PK/PD principles for patients with HAP who fall into various clinical or sociodemographic subgroups is not known. This is a critical deficiency in the evidence base that future research needs to address directly. Specifically, 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 mimimum inhibitory concentration (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.

The gaps in understanding the links among patient-specific factors, organism MIC, antibiotic dose, and clinical outcomes reflect the difficulty in isolating these variables and establishing cause-effect relationships. Elevated organism MICs and, thus, antibiotic regimen and dosing choices may be correlated with disease severity without having a causal effect. Furthermore, unmeasured organism factors such as virulence determinants, which may be associated with elevated MICs, may play a role in patient outcomes. These potential confounding variables should be considered when drawing conclusions about the effects of antibiotic dose optimization on patient outcomes.[70-72]

Finally, another hole in the evidence is whether optimizing PK in dosing strategies in the clinical setting can 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 today's 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 primary goals of such investigations are (1) to document the impact of different dosing strategies on meaningful clinical and patient-centered endpoints, such as survival in different patient populations, and (2) to determine their effects on the development of antibiotic resistance in bacteria. In addition, such studies can provide important data on other outcomes of interest to both clinicians and patients; these include ventilator days, rates of relapse, rates of reinfection, mortality risk, and timeliness of laboratory results in terms of being clinically useful in managing treatment.

Measuring microbiological outcomes such as eradication of bacteria, microbiologic relapse, decrease in colony counts of culture, and development of antibiotic resistance can also yield information useful for developing dosing guidelines and recommendations. For certain patient-centered outcomes, such as clinical response and treatment failure not otherwise explained, clearly identifying how the investigators defined those outcomes (e.g., clinician judgment of patient signs and symptoms, laboratory values, quality of life assessed through patient self-reports, or mortality as measured at specific points in time) will improve interpretation of the findings. We believe research teams should be precise in delineating their conceptualization of all such outcomes.

Although antibiotic resistance clearly can arise during or from antibiotic treatment, less is known about the relationships among drug dosage, PK/PD optimization, and the development of resistance. Evaluating either the development or the prevention of resistance is a difficult research endeavor. Nevertheless, investigators can institute several approaches such as monitoring resistance trends in individual patients or tracking changes in hospital or local susceptibility patterns over time. Metrics for evaluating the development of resistance should be tested and validated in relationship to meaningful clinical and ultimate health outcomes. Researchers mounting PK/PD studies would then have more reliable and valid ways to examine this very important public health concern.

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Appendix A. Exact Search Strings

Medline® Search Update June 7, 2014

Search	Query	Items found
#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])	132945
#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 facililty”[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])	1576325
#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])	149630
#4	Search (#1 AND (#2 OR #3))	48199
#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 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])	5862674
#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 “AUIC”[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])	499130

#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 ofloxacine[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 “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])	386774
#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])	655101
#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])	1623787
#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])	128163
#11	Search (#4 AND (#5 OR #6) AND (#7 OR #8)))	4540
#12	Search (#11 NOT (#9 OR #10))	4340
#13	Search (#11 NOT (#9 OR #10)) Filters: Humans	3558
#14	Search (#11 NOT (#9 OR #10)) Filters: Other Animals	921
#15	Search (#14 NOT #13)	586
#16	Search (#12 NOT #15)	3754
#17	Search (#12 NOT #15) Filters: English	2864
#18	Search (#12 NOT #15) Filters: English; Adult: 19+ years	1298
#19	Search (#12 NOT #15) Filters: Publication date from 2012/10/30; English; Adult: 19+ years	**94**
#20	Search ((#11 AND (“retraction”[All Fields] OR “Retracted Publication”[pt])	1

Cochrane Search Update 6/8/14

63 results – 62 imported

ID	Search	Hits
#1	[mh Pneumonia]	2562
#2	[mh "Pneumonia, Bacterial"]	682
#3	[mh "Pneumonia, Ventilator-Associated"]	200
#4	'pneumonia' or 'pneumonia bacterial' or 'lung inflammation' or 'pulmonary inflammation' or 'pneumonias' or 'pneumonitis' or 'pneumonitides'	8925
#5	#1 or #2 or #3 or #4	8965
#6	[mh "Nursing Homes"]	1018
#7	[mh "Skilled Nursing Facilities"]	53
#8	[mh "Intermediate Care Facilities"]	15
#9	[mh "Drug Resistance, Bacterial"]	800
#10	[mh "Critical Care"]	1844
#11	[mh "[Intensive Care"]	1151
#12	[mh "Gram-Positive Bacterial Infections"]	4904
#13	[mh "Gram-Negative Bacterial Infections"]	5762
#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 facililty' 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'	84802
#15	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	91608
#16	[mh Sepsis]	3046
#17	[mh Bacteremia]	748
#18	[mh Endotoxemia]	133
#19	[mh "Hemorrhagic Septicemia"]	0
#20	[mh "Shock, Septic"]	429
#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’	7733
#22	#16 or #17 or #18 or #19 or #20 or #21	8312
#23	#5 and (#15 or #22)	4887
#24	[mh Pharmacokinetics]	10527
#25	[mh "Drug Monitoring"]	1095
#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'	192588
#27	#24 or #25 or #26	192979
#28	[mh "Dose-Response Relationship, Drug"]	24746
#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'	48751
#30	#28 or #29	48751
#31	'vancomycin' or 'carbapenems' or 'thienamycins' or 'cephalosporins' or '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 'aclarubicin' 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 ofloxacine 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' 21899

#32 [mh "Anti-Bacterial Agents"] 9205

#33 'anti-bacterial agent' or 'anti-bacterial agents' or 'antibacterial agent' or 'antibacterial agents' or antibiotic* 22025

#34 #31 or #32 or #33 34313

#35 #23 and (#27 or #30) and #34 1205

#36 #35 Publication Year from 2012 to 2014, in Trials **63**

IPA Search Update 6/8/14 (15 retrieved – all imported)

#	Query	Limiters/Expanders	Last Run Via	Results
S36	S35	Limiters - Published Date: 20121001-20141231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	15
S35	S23 and (S27 OR S30) and S34	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	289
S34	S31 OR S32 OR S33	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	42,296
S33	TX “anti-bacterial agent” OR “anti-bacterial agents” OR “antibacterial agent” OR “antibacterial agents” OR antibiotic*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	27,509
S32	SU AntiBacterial Agents	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	1,026
S31	TX “vancomycin” OR “carbapenems” OR “thienamycins” OR “cephalosporins” OR “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 “aclarubicin” 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	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	26,994

#	Query	Limiters/Expanders	Last Run Via	Results
	"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 ofloxacine 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"			
S30	S28 OR S29	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	22,451
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"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	22,442
S28	SU Dose-Response Relationship	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	9
S27	S24 OR S25 OR S26	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	87,860
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	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	87,061

#	Query	Limiters/Expanders	Last Run Via	Results
	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"			
S25	SU Drug Monitoring	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	1,017
S24	SU Pharmacokinetics	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	46,035
S23	S5 AND (S15 OR S22)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	1,439
S22	S16 OR S17 OR S18 OR S19 OR S20 OR S21	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	3,300
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"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	3,293
S20	SU Septic Shock	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	98
S19	SU Hemorrhagic Shock	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	7

#	Query	Limiters/Expanders	Last Run Via	Results
S18	SU Endotoxemia	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	34
S17	SU Bacteremia	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	329
S16	SU Sepsis	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	834
S15	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	29,558
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” OR “healthcare associated” OR “ventilator associated” OR “cross infection” OR “nursing home” OR “nursing homes” OR “intermediate care facililty” 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”	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	29,510
S13	SU Gram-Negative Bacterial Infections	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	157
S12	SU Gram-Positive Bacterial Infections	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	215
S11	SU Intensive Care Unit	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases	1,824

#	Query	Limiters/Expanders	Last Run Via	Results
			Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	
S10	SU Critical Care	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	2,062
S9	SU Drug Resistance	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	241
S8	SU Intermediate Care Facilities	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	17
S7	SU Skilled Nursing Facilities	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	125
S6	SU Nursing Homes	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	925
S5	S1 OR S2 OR S3 OR S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	4,000
S4	TX “pneumonia” OR “pneumonia bacterial” OR “lung inflammation” OR “pulmonary inflammation” OR “pneumonias” OR “pneumonitis” OR “pneumonitides”	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	4,000
S3	SU Ventilator-Associated Pneumonia	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	2
S2	SU Bacterial Pneumonia	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	18
S1	SU Pneumonia	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	2,274

Medline® Search Update 10/30/13

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]))	128,649
#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])	1,523,261
#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])	144,734
#4	Search (#1 AND (#2 OR #3))	46,515
#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 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]))	5,713,972
#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 “AUIC”[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]))	485,405
#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]	377,175

Search	Most Recent Queries	Result
	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 ofloxacine[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 “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]))	634,169
#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]))	1,565,573
#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]))	115,455
#11	Search (#4 AND (#5 OR #6) AND (#7 OR #8))	4,349
#12	Search (#11 NOT (#9 OR #10))	4,157
#13	Search (#11 NOT (#9 OR #10)) Filters: Humans	3,437
#14	Search (#11 NOT (#9 OR #10)) Filters: Other Animals	878
#15	Search (#14 NOT #13)	562
#16	Search (#12 NOT #15)	3,595
#17	Search (#12 NOT #15) Filters: English	2,722
#18	Search (#12 NOT #15) Filters: English; Adult: 19+ years	1,247
#19	Search (#12 NOT #15) Filters: Publication date from 2012/05/15 to 2013/12/31; English; Adult: 19+ years	75
#20	Search (#11 AND (“retraction”[All Fields] OR “Retracted Publication”[pt]))	1

Cochrane Search Update 10/30/13

ID	Search	Hits
#1	MeSH descriptor: [Pneumonia] explode all trees	2,450
#2	MeSH descriptor: [Pneumonia, Bacterial] explode all trees	654
#3	MeSH descriptor: [Pneumonia, Ventilator-Associated] explode all trees	170
#4	'pneumonia' or 'pneumonia bacterial' or 'lung inflammation' or 'pulmonary inflammation' or 'pneumonias' or 'pneumonitis' or 'pneumonitides'	7,677
#5	#1 or #2 or #3 or #4	7,717
#6	MeSH descriptor: [Nursing Homes] explode all trees	915
#7	MeSH descriptor: [Skilled Nursing Facilities] explode all trees	52
#8	MeSH descriptor: [Intermediate Care Facilities] explode all trees	14
#9	MeSH descriptor: [Drug Resistance, Bacterial] explode all trees	749
#10	MeSH descriptor: [Critical Care] explode all trees	1,693
#11	MeSH descriptor: [Intensive Care] explode all trees	1,047
#12	MeSH descriptor: [Gram-Positive Bacterial Infections] explode all trees	4,608
#13	MeSH descriptor: [Gram-Negative Bacterial Infections] explode all trees	5,532
#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'	74,453
#15	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	80,926
#16	MeSH descriptor: [Sepsis] explode all trees	2,832
#17	MeSH descriptor: [Bacteremia] explode all trees	700
#18	MeSH descriptor: [Endotoxemia] explode all trees	125
#19	MeSH descriptor: [Hemorrhagic Septicemia] explode all trees	0
#20	MeSH descriptor: [Shock, Septic] explode all trees	389
#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’	6,835
#22	#16 or #17 or #18 or #19 or #20 or #21	7,382
#23	#5 and (#15 or #22)	4,263
#24	MeSH descriptor: [Pharmacokinetics] explode all trees	9,833
#25	MeSH descriptor: [Drug Monitoring] explode all trees	958
#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'	173,487
#27	#24 or #25 or #26	173,838
#28	MeSH descriptor: [Dose-Response Relationship, Drug] explode all trees	23,367
#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'	44,156

ID	Search	Hits
#30	#28 or #29	44,156
#31	'vancomycin' or 'carbapenems' or 'thienamycins' or 'cephalosporins' or '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 'aclarubicin' 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 ofloxacine 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'	20,769
#32	MeSH descriptor: [Anti-Bacterial Agents] explode all trees	8,537
#33	'anti-bacterial agent' or 'anti-bacterial agents' or 'antibacterial agent' or 'antibacterial agents' or antibiotic*	20,299
#34	#31 or #32 or #33	31,927
#35	#23 and (#27 or #30) and #34 Limit: from 2012, in Trials	21

IPA Search Update 10/30/13

#	Query	Results
S1	SU Pneumonia	2,231
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”	3,918
S5	S1 OR S2 OR S3 OR S4	3,918
S6	SU Nursing Homes	919
S7	SU Skilled Nursing Facilities	125
S8	SU Intermediate Care Facilities	17
S9	SU Drug Resistance	237
S10	SU Critical Care	2,032
S11	SU Intensive Care Unit	1,783
S12	SU Gram-Positive Bacterial Infections	210
S13	SU Gram-Negative Bacterial Infections	150
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” OR “healthcare associated” OR “ventilator associated” OR “cross infection” OR “nursing home” OR “nursing homes” OR “intermediate care facililty” 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”	28,805
S15	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14	28,853
S16	SU Sepsis	807
S17	SU Bacteremia	312

#	Query	Results
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”	3,221
S22	S16 OR S17 OR S18 OR S19 OR S20 OR S21	3,228
S23	S5 AND (S15 OR S22)	1,401
S24	SU Pharmacokinetics	45,001
S25	SU Drug Monitoring	1,014
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”	93,595
S27	S24 OR S25 OR S26	94,350
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”	21,920
S30	S28 OR S29	21,929
S31	TX “vancomycin” OR “carbapenems” OR “thienamycins” OR “cephalosporins” OR “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 “aclarubicin” 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 ofloxacine 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”	26,609
S32	SU AntiBacterial Agents	1,026
S33	TX “anti-bacterial agent” OR “anti-bacterial agents” OR “antibacterial agent” OR “antibacterial agents” OR antibiotic*	27,023
S34	S31 OR S32 OR S33	41,641
S35	S23 and (S27 OR S30) and S34	284
S36	S35 Limiters – Published Date 20090101-20131231	78
S37	S35 Limiters – Published Date 20120101-20131231	7

Original Searches 5/15/2013

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])	125,685
#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 facililty”[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]	1,487,227
#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]	141,016
#4	Search (#1 AND (#2 OR #3))	45,371
#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 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])	5,605,147
#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 “AUIC”[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])	475,113
#7	Search (Vancomycin[mesh] OR vancomycin[all fields] OR Carbapenems[all fields] OR	370,705

Search	Most Recent Queries	Result
	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 ofloxacine[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 "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])	621,086
#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])	1,527,036
#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])	107,278
#11	Search (#4 AND (#5 OR #6) AND (#7 OR #8))	4,233
#12	Search (#11 NOT (#9 OR #10))	4,048
#13	Search (#11 NOT (#9 OR #10)) Filters: Humans	3,356
#14	Search (#11 NOT (#9 OR #10)) Filters: Other Animals	850
#15	Search (#14 NOT #13)	547
#16	Search (#12 NOT #15)	3,501

Search	Most Recent Queries	Result
#17	Search (#16) Filters: English	2,636
#18	Search (#16) Filters: English; Adult: 19+ years	1,213

Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Pneumonia] explode all trees	2,406
#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'	7,518
#5	#1 or #2 or #3 or #4	7,588
#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
#10	MeSH descriptor: [Critical Care] explode all trees	1,668
#11	MeSH descriptor: [Intensive Care] explode all trees	1,029
#12	MeSH descriptor: [Gram-Positive Bacterial Infections] explode all trees	4,508
#13	MeSH descriptor: [Gram-Negative Bacterial Infections] explode all trees	5,475
#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 facililty' 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'	72,654
#15	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	79,030
#16	MeSH descriptor: [Sepsis] explode all trees	2,788
#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’	6,717
#22	#16 or #17 or #18 or #19 or #20 or #21	7,257
#23	#5 and (#15 or #22)	4,159
#24	MeSH descriptor: [Pharmacokinetics] explode all trees	9,715
#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'	170,788

ID	Search	Hits
#27	#24 or #25 or #26	171,127
#28	MeSH descriptor: [Dose-Response Relationship, Drug] explode all trees	23,091
#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'	43,464
#30	#28 or #29	43,464
#31	'vancomycin' or 'carbapenems' or 'thienamycins' or 'cephalosporins' or '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 'aclarubicin' 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 ofloxacine 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'	20,530
#32	MeSH descriptor: [Anti-Bacterial Agents] explode all trees	8,388
#33	'anti-bacterial agent' or 'anti-bacterial agents' or 'antibacterial agent' or 'antibacterial agents' or antibiotic*	19,974
#34	#31 or #32 or #33	31,453
#35	#23 and (#27 or #30) and #34	1,080
#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” OR “healthcare associated” OR “ventilator associated” OR “cross infection” OR “nursing home” OR “nursing homes” OR “intermediate care facililty” OR “intermediate care facilities” OR “skilled nursing facility” OR	28,294

#	Query	Results
	"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 "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 "aclarubicin" 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 ofloxacine 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"	26,345
S32	SU Anti-Bacterial Agents	19,600

#	Query	Results
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.

For this systematic review (SR), 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.

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 (respectively) provide 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?
Hanes et al., 2000[1]	Unclear or not reported	No	No	Yes	No	No	Unclear or not reported
Jaruratanasirikul, 2012[2]	Yes	No	No	Only 11 pts, mostly male, varying renal function	No	No	Yes
Nicolau, 1999[3]	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[4]	Unclear or NR	No	No	Yes	No	No mention of blinding	No mention of blinding
Nicolau, 2001[5] McNabb, 2001[6]	Unclear or NR	No	No	Yes	No	Not blinded (open label)	Not blinded (open label)
Sakka, 2007[7]	Yes	Unclear or NR	Unclear or NR	Yes	Unclear or NR	Not blinded	Not blinded
Wang, 2009[8]	Unclear or not reported	No	No	Yes, but very few baseline characteristics reported	No	No	Unclear or not reported

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., ≥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?
Hanes et al., 2000[1]	Unclear or not reported	No	No	No	Unclear or not reported	Yes
Jaruratanasirikul, 2012[2]	No	No	No	No	No	Yes
Nicolau, 1999[3]	Unclear or NR	No	No	Yes	No	Yes
Nicolau, 1999[4]	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Yes
Nicolau, 2001[5] McNabb, 2001[6]	Yes	No	No	No	No	Yes
Sakka, 2007[7]	No	Unclear or NR	No	No	No	Yes
Wang, 2009[8]	Unclear or not reported	Unclear or not reported	Unclear or not reported		Unclear or not reported	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
Hanes et al., 2000[1]	Yes	Yes	Unclear or not reported	Yes	Medium	
Jaruratanasirikul, 2012[2]	Not evaluated	Not evaluated	Unclear or not reported	Yes	High	Very small number of patients. High risk of selection, measurement bias, and confounding.
Nicolau, 1999[3]	NA	NA	Unclear or NR	Yes	Medium	
Nicolau, 1999[4]	NA	NA	Unclear or NR	Yes	Medium	
Nicolau, 2001[5] McNabb, 2001[6]	Yes	Yes	Yes	Yes	Medium	
Sakka, 2007[7]	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.
Wang, 2009[8]	Yes	Yes	Unclear or not reported	Yes	Medium	

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?
Fahimi et al., 2012[9]	Unclear or not reported	Yes	Unclear or not reported	No	No	Not applicable	Yes
Lorente, 2009[10]	No	Yes	Unclear or NR	NA	NA	NA	Yes
Scaglione, 2009[11]	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
Fahimi et al., 2012[9]	Yes	Yes	Not reported	Yes	No	Medium	
Lorente, 2009[10]	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.

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

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
Scaglione, 2009[11]	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

Exclusion Codes:

1 - Not available in English
2 - Wrong Outcome(s)
3 - Wrong or No Intervention
4 - Wrong Population
5 - Wrong Publication Type
6 - Wrong Study Design
7 - Wrong Comparison or No Comparison
8 - Does Not Answer a KQ

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3. Alvarez-Lerma F, Insausti-Ordeñana J, Jordá-Marcos R, et al. Efficacy and tolerability of piperacillin/tazobactam versus ceftazidime in association with amikacin for treating nosocomial pneumonia in intensive care patients: a prospective randomized multicenter trial. Intensive Care Med. 2001(3):493-502. PMID: CN-00355757. Exclusion Code: 3.
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5. Bagg R. Antibiotic treatment of staphylococcal pneumonia in adults. J Antimicrob Chemother. 1978 Jul;4(4):297-9. PMID: 308503. Exclusion Code: 5.
6. Balderson BJ, Yates ME, Patil NP, et al. Evaluation of doripenem utilization and susceptibilities at a large urban hospital. Int J Clin Pharm. 2011 Dec;33(6):958-63. PMID: 21984226. Exclusion Code: 4.
7. Bartel K, Habash T, Lugauer S, et al. Optimal tobramycin dosage in patients with cystic fibrosis--evidence for predictability based on previous drug monitoring. Infection. 1999;27(4-5):268-71. PMID: 10885841. Exclusion Code: 4.
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13. Benko R, Matuz M, Doro P, et al. Pharmacokinetics and pharmacodynamics of levofloxacin in critically ill patients with

ventilator-associated pneumonia. Int J Antimicrob Agents. 2007 Aug;30(2):162-8. PMID: 17570646. Exclusion Code: 7.

14. Bernhardt LL. Cefadroxil in the treatment of lobar pneumonia. J Int Med Res. 1980;8(Suppl 1):98-100. PMID: 7439514. Exclusion Code: 3.

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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
Fahimi et al., 2012[1] India	Prospective cohort	Analyzed: G1: Continuous infusion: 31 G2: Intermittent infusion: 30 9 patients expired on day 8 and did not complete the study protocol to the final analysis	ICU	All of the following criteria were necessary for diagnosis of VAP: white blood cell count >10,000 cells/mm3 or <4000 cells/ mm3; body temperature >38°C or <35.5°; new onset of purulent sputum or a change in sputum character; chest radiography indicating new or progressive infiltrate and a significant quantitative pathogen culture from respiratory secretions (tracheal aspirate >106 colony-forming units/mL or growth of ≥104 colony-forming units/mL of microorganism on bronchoscopic broncho alveolar lavage (BAL) culture) or isolation of the same microorganism in blood and respiratory secretions on Day 3 and Day 8. All of them should be older than 18 years, and the estimated length of ventilation is greater than 48 h. The presence of Gram negative bacteria was verified by a significant quantitative culture from respiratory secretions	Exclusion criteria were hypersensitivity or allergy to b-lactam antibiotics, pregnancy or lactation, neutropenia (<1000 cells/ mm3), acquired immunedeficiency syndrome (AIDS), glomerular filtration rate (GFR) <60 mL/min by the Cockcroft–Gault equation, solid or hematological tumor and finding of any other known source of infection such as early-onset hospital-acquired pneumonia (HAP) or health-care-associated pneumonia (HCAP) without any risk factors for multidrug-resistant (MDR) pathogens according to the VAP guidelines	No funding source

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
Hanes et al., 2000[2] United States	RCT	Randomized: G1: Continuous infusion: 18 G2: Intermittent infusion: 15 Analyzed: G1: Continuous infusion: 17 G2: Intermittent infusion: 14 G1: One patient excluded from outcome analysis due to A. calcoaceticus pneumonia intermediately sensitive to ceftazidime G2: one patient excluded from all analyses due to concomitant Enterococcus urinary tract infection from initial cultures	ICU	Patients aged 16 to 65 years with Gram-negative nosocomial pneumonia occurring more than 48 hours after admission were screened for entry into the study. Nosocomial pneumonia was defined as temperature .100.4°F, white blood cell count $ 10,000 mm3, new or progressing infiltrate on chest x-ray film or rales/dullness to percussion on physical examination, and the presence of ≥10^5 colony-forming units/mm3 on bronchoalveolar lavage fluid culture.	Patients were excluded if they had a known sensitivity to cephalosporins, an estimated creatinine clearance of ,30 mL/min, or if the causative bacterial pathogen was resistant to ceftazidime. This study was approved by the University of Tennessee Institutional Review Board and written, informed consent was obtained from the patient or legal representative	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
Jaruratanasirikul et al., 2012[3] Thailand	RCT	NR	ICU	Patients were eligible for the study if they met the following criteria: (i) >18 years of age; (ii) intubated and receiving mechanical ventilation for ≥48 h; and (iii) clinical suspicion of VAP, defined by a new and persistent infiltrate on chest radiography associated with at least one of the following: purulent tracheal secretions; temperature of ≥38.3 ◦C; or a leucocyte count >10 000 cells/mm3	Patients were excluded from the study if they were pregnant or in circulatory shock (defined as a systolic blood pressure of 90 mmHg and poor tissue perfusion) or had documented hypersensitivity to carbapenems or an estimated creatinine clearance (CLCr) (determined by the Cockcroft–Gault method) [9] of <50 mL/min. The severity of illness of each patient was assessed at the time of enrolment into the study using Acute Physiology and Chronic Health Evaluation (APACHE) II scores and the Sepsis-related Organ Failure Assessment (SOFA) score. Diagnosis of VAP was also evaluated by the Clinical Pulmonary Infection Score (CPIS)	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
Lorente, 2009[4] 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/mm3 or <4000 cells/mm3; and a significant quantitative pathogen culture from respiratory secretions (tracheal aspirate >106 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[5] 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[6] 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 isolatuion 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[7] McNabb, 2001[8] 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/mm3) 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[9] 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 edotracheal 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[10] 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 aminoglycides, fluoroquinolones, or beta lactams; and at least two of the following: cough, purulent sputum, ausculatory findings of pneumonia, dypsnea, tachpena 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

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
Wang., 2009[11] China	RCT	Randomized G1: Continuous infusion: 15 G2: Intermittent infusion: 15	ICU	Diagnosed with HAP according to standard clinical criteria and due to MDR A. baumannii, as cultured from the samples of endotracheal aspirate and the brochoalveolar lavage	NR	No funding sources

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; mm^3, 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
Fahimi et al., 2012[1]	Ventilator-acquired pneumonia (HAP and HCAP patients excluded) G1: Continuous infusion G2: Intermittent infusion	Baseline APACHE II Score upon ICU admission, mean (SD) G1: 18.87 (5.95) G2: 20.43 (6.17) p=0.319	Total: 53.81 (21.77) G1: 49.41 (20.84) G1: 58.36 (22.11)	Total: 31 (50.8) G1: 15 (48.4) G2: 16 (53.3)	NR	Cardiac and vascular disorders, n (%) G1: 10 (32.3) G1: 9 (30) p=0.85 Pulmonary disorders, n (%) G1: 17 (56.7) G2: 18 (58.1) p=0.91
Hanes et al., 2000[2]	Nosocomial pneumonia G1: Continuous infusion G2: Intermittent infusion	Baseline APACHE II Score, Mean (SD) G1: 12.8 (4.6) G2: 10.9 (5.8)	G1: 33.5 (12.5) G2: 36.1 (12.8)	Total: 16 (19) G1: 3 (17.6) G2: 3 (21.4)	NR	Mean CLCr, mL/min (SD) G1: 96.8 (23.3) G2: 96.8 (21.6) p=NS
Jaruratanasirikul et al., 2012[3]	Ventilator-acquired pneumonia G1: Continuous infusion G2: Intermittent infusion	Baseline APACHE II Score, Mean (SD) G1: NR G2: NR	Total: 50 (16) Range: 25 to 80 years) G1: NR G2: NR	Total: NR (10) G1: NR G2: NR	NR	NR

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
Lorente, 2009[4]	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[5]	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[6]	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[7] McNabb, 2001[8]	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[9]	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[10]	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

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
Wang., 2009[11]	Hospital-acquired pneumonia G1: Continuous infusion G2: Intermittent infusion	Baseline APACHE[12] II Score, mean (SD) G1: 20.33 (4.29) G2: 17.33 (5.82)	G1: 43.33 (21.02) G2: 39.67 (21.62)	Total: 11 (36.7) G1: 5 (33.33) G2: 6 (40.0)	NR	NR

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
Fahimi et al., 2012[1]	Prolonged or continuous infusion	Piperacillin 3 g//tazobactam 0.375 g by continuous infusion every 8 hours for 4 hours	Bolus dosing	Piperacillin 3 g//tazobactam 0.375 g by intermittent infusion every 6 hours for 30 minutes
Hanes et al., 2000[2]	Prolonged or continuous infusion	Ceftazidime 2 g as an intravenous bolus followed by 60 mg/kg per day as a continuous intravenous infusion. Each 2-g ceftazidime dose was administered over 30 minutes	Bolus dosing	Ceftazidime 2 g intravenously every 8 hours
Jaruratanasirikul et al., 2012[3]	Prolonged or continuous infusion	Doripenem 4 hour infusion of 0.5 g diluted in 100 mL of normal saline solution via an infusion pump at a constant flow rate every 8 hours for seven doses	Bolus dosing	Doripenem 1 hour infusion of 0.5 g diluted in 100 mL of normal saline solution via an infusion pump at a constant flow rate every 8 hours for seven doses
Lorente, 2009[4]	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[5]	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[6]	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[7] McNabb, 2001[8]	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

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

Author, Year	Intervention Type	Description of Intervention	Comparator Type	Description of Comparator
Sakka, 2007[9]	Continuous infusion	Continuous imipenem 7g/cilastatin 7g administered over 72 h, following a loading dose of of imipenem 1g/cilastin 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[10]	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
Wang., 2009[11]	Prolonged or continuous infusion	Extended-infusion meropenem 500 mg every 6 hours over 3 hour infusion	Bolus dosing	Intravenous meropenem 1 g every 8 hours over a 1 hour infusion

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
Fahimi et al., 2012[1]	G1: Piperacillin/ tazobactam continuous infusion (n=31) G2: Piperacillin/ tazobactam intermittent infusion (n= 30)	Clinical pulmonary infection score	Clinical pulmonary infection score Day 1 G1: 7.12 (1.33) G2: 6.96 (1.77) p=0.687 Day 3 G1: 8.74 (1.76) G2: 8.66 (2.48) p=0.892 Day 8 G1: 8.51 (2.07) G2: 8.60 (2.22) p=0.880	Duration of mechanical ventilation days	Duration of mechanical ventilation days : G1: 42.61 (29.10) G2: 37.96 (28.23) p=0.529
Hanes et al., 2000[2]	G1: Ceftazidime continuous infusion: (n=17) G2: Ceftazidime intermittent infusion: (n=14)	Cure Definition: complete resolution of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on the chest radiograph	Cure: G1: NR (56) G2: NR (71) p=0.63	Duration of mechanical ventilation days	Duration of mechanical ventilation days: G1: 22.9 (19.9) G2: 13.3 (6.1) p=0.16
Jaruratanasirikul et al., 2012[3]	G1: Doripenem continuous infusion (n=NR) G2: Doripenem intermittent infusion (n=NR)	NR	NR	NR	NR
Lorente, 2009[4]	G1: Piperacillin/ tazobactam continuous infusion (n=37) G2: Piperacillin/ tazobactam intermittent infusion (n=46)	NR	NR	NR	NR
Nicolau, 1999[5]	G1: Ceftazidime intermittent infusion (n=17) G2: Ceftazidime continuous infusion (N=17)	NR	NR	NR	NR

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
Nicolau, 1999[6]	G1: Ceftazidime intermittent infusion (n=13) G2: Ceftazidime continuous infusion (n=11)	NR	NR	NR	NR
Nicolau, 2001[7] McNabb, 2001[8]	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
Sakka, 2007[9]	G1: Continuous imipenem/ cilastatin (n=10) G2: Intermittent imipenem/ cilastatin (n=10)	NR	NR	NR	NR

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
Scaglione, 2009[10]	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
Wang., 2009[11]	G1:Continuous meropenem (n=15) G2: Intermittent meropenem (n= 15)	Success: CPIS <6	Success: Day 3 G1: 5 (33.33) G2: 6 (40) Day 5 G1: 14 (93.33) G2: 13 (86.67) Day 7 G1: 15 (100) G2: 15 (100)	NR	NR

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
Fahimi et al., 2012[1]	G1: Piperacillin/ tazobactam continuous infusion continuous infusion: (n=31) G2: Piperacillin/ tazobactam intermittent infusion (n= 30)	NR	G1: 17 (54.8%) G2: 20 (66.7%)	NR	NR
Hanes et al., 2000[2]	G1: Ceftazidime continuous infusion (n= 17) G2: Ceftazidime intermittent infusion (n= 14)	Death due to pneumonia	NR	Pneumonia superinfection (most commonly caused by *A calcoaceticus*)	G1: NR (44) G2: NR (2) p=NR Within treatment failures G1: NR (71) G2: NR (75) p=NR NR
Jaruratanasirikul et al., 2012[3]	G1: Doripenem continuous infusion (NR) G2: Doripenem intermittent infusion (NR)	NR	NR	NR	NR
Lorente, 2009[4]	G1: Piperacillin/ tazobactam continuous infusion (n=37) G2: Piperacillin/ tazobactam intermittent infusion (n=46)	NR	NR	NR	NR
Nicolau, 1999[5]	G1: Ceftazidime intermittent infusion (n=17) G2: Ceftazidime continuous infusion (n=17)	NR	NR	NR	NR
Nicolau, 1999[6]	G1: Ceftazidime intermittent infusion (n=13) G2: Ceftazidime continuous infusion (n=11)	NR	NR	NR	NR

Table D-5. Morbidity and mortality outcomes (continued)

Author, Year	Intervention and Comparator Groups	Mortality – Definition	Mortality – Results	Morbidity – Definition	Morbidity – Results
Nicolau, 2001[7] McNabb, 2001[8]	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[9]	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[10]	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
Wang., 2009[11]	G1:Continuous meropenem (n=15) G2: Intermittent meropenem (n= 15)	NR	NR	NR	NR

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
Fahimi et al., 2012[1]	G1: Piperacillin/ tazobactam continuous infusion continuous infusion: (n=31) G2: Piperacillin/ tazobactam intermittent infusion (n= 30)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hanes et al., 2000[2]	G1: Ceftazidime continuous infusion (n= 17) G2: Ceftazidime intermittent infusion (n= 14)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

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
Jaruratanasirikul et al., 2012[3]	G1: Doripenem continuous infusion (NR) G2: Doripenem intermittent infusion (NR)	NR	NR	NR	NR	NR	NR	NR	NR	NR	G1: authors stated well tolerated and no reported adverse events G2: authors stated well tolerated and no reported adverse events
Lorente, 2009[4]	G1: Piperacillin/ tazobactam continuous infusion (n=37) G2: Piperacillin/ tazobactam intermittent infusion (n=46)	NR	NR	NR	NR	NR	NR	Antibiotic resistance developing during the course of treatment	N with outcome: G1: 0 G2: 0	NR	NR

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, 1999[5]	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[6]	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
Nicolau, 2001[7] McNabb, 2001[8]	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 determi-nation (i.e. enrollment specimen)	N with outcome: G1: 18 G2: 17	NR	NR

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
Sakka, 2007[9]	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[10]	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
Wang., 2009[11]	G1:Continuous meropenem (n=15) G2: Intermittent meropenem (n= 15)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

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

References for Appendix D

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