Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department With Community-Acquired Pneumonia

From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Community-Acquired Pneumonia:
Devorah J. Nazarian, MD, Chair
Orin L. Eddy, MD
Thomas W. Lukens, MD, PhD
Scott D. Weingart, MD
Wyatt W. Decker, MD

Approved by the ACEP Board of Directors, June 23, 2009

Supported by the Emergency Nurses Association, July 21, 2009

0196-0644/$-see front matter

doi:10.1016/j.annemergmed.2009.07.002

[Ann Emerg Med. 2009;54:704-731.]

ABSTRACT

This clinical policy from the American College of Emergency Physicians focuses on critical issues concerning the management of adult patients presenting to the emergency department (ED) with community-acquired pneumonia. It is an update of the 2001 clinical policy for the management and risk stratification of adult patients presenting to the ED with community-acquired pneumonia. A subcommittee reviewed the current literature to derive evidence-based recommendations to help answer the following questions: (1) Are routine blood cultures indicated in patients admitted with community-acquired pneumonia? (2) In adult patients with community-acquired pneumonia without severe sepsis, is there a benefit in mortality or morbidity from the administration of antibiotics within a specific time course? The evidence was graded and recommendations were given based on the strength of evidence.

INTRODUCTION

Community-acquired pneumonia (CAP) is a major health problem in the United States. CAP is the seventh leading cause of death in the United States, with 1.7 million hospital admissions per year.[1,2] The annual economic costs of CAP-related hospitalizations have been estimated at $9 billion.[3] Pneumonia carries an age-adjusted mortality rate up to 22%.[1] Despite clinical advances, pneumonia mortality rates have not decreased significantly since penicillin became routinely available.[4]

Pneumonia can be divided into 4 categories based on the site of acquisition of illness: CAP, hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and health care-associated pneumonia (HCAP).[5] CAP has recently been defined as an acute pulmonary infection in a patient who is not hospitalized or living in a long-term care facility 14 or more days before presentation and does not meet the criteria for HCAP.[5] HAP is defined as a new infection occurring 48 hours or longer after hospital admission. VAP is defined as pneumonia occurring 48 to 72 hours after endotracheal intubation. HCAP encompasses many patients previously defined as having CAP. HCAP is defined as infection occurring within 90 days of a 2-day or longer hospitalization; in a nursing home or long-term care residence; within 30 days of receiving intravenous antibacterial therapy, chemotherapy, or wound care or after a hospital or hemodialysis clinic visit; or in any patient in contact with a multidrug-resistant pathogen.[6] An emerging body of evidence suggests that patients with HCAP more closely resemble patients with HAP and may require HAP-like treatments.[6-8]

Given the significance of CAP, improving pneumonia care has become a recent focus of many organizations such as The Joint Commission and the Centers for Medicare & Medicaid Services (CMS). There are a number of core measures for patients admitted with the diagnosis of pneumonia. Core measures that evaluate the emergency department (ED) care of CAP patients include blood culture collection prior to first antibiotic administration (when ED blood cultures are drawn), administration of initial antibiotics within 6 hours of ED arrival (previously within 4 hours), and appropriate antibiotic selection.[9]

To comply with antibiotic quality measures and CMS and private payer pay for performance programs, some EDs have moved toward treating possible CAP patients with antibiotics before the diagnosis is confirmed.[10] In this age of increasing antibiotic resistance, this may have negative consequences in excess of any putative benefit. Kanwar et al[11] studied 2 cohorts of patients with the ED diagnosis of CAP, before and after the implementation of antibiotic timing guidelines. To achieve an increase in the number of patients with time to first antibiotic dose less than 4 hours, an additional 17% of patients were unnecessarily treated with antibiotics. Khalil et al[12] performed a retrospective analysis of factors associated with the eventual diagnosis of CAP in patients presenting to the ED. Of 1,948 patients who presented with respiratory complaints, only 198 eventually were diagnosed with CAP. If half of the patients in this study received empiric antibiotics, at least 40% of the patients would have received antibiotics unnecessarily, potentially increasing antibiotic resistance in the community. In an online questionnaire, Pines et al[10] found that 37% of academic EDs administer antibiotics before obtaining chest radiograph. In a retrospective chart review of patients admitted with pneumonia, 22% of the patients presented in a manner that can result in delayed antibiotics delivery as a result of diagnostic uncertainty.[13] The most recent iteration of the CMS guidelines includes provisions for diagnostic uncertainty when assessing time to first antibiotic dose. With the current ED crowding crisis, the feasibility of rapid antibiotic administration can be difficult.[14-16]

The disposition of patients with pneumonia is a major decision for emergency physicians, with impact on patient outcome. Prognostic tools such as the Pneumonia Severity Index (PSI) and severity-of-illness indexes such as the CURB and CURB-65 scores have been validated in several studies and can be used to aid in admission decisions.[17,18] The PSI stratifies patients into 5 categories on the basis of mortality risk. It has been suggested that patients in groups I and II be treated as outpatients, those in group III be treated in an observation unit or with a short hospitalization, and those patients who fall into groups IV and V be admitted for treatment.[19] CURB-65 is an easy-to-use severity-of-illness score that uses the following factors as indicators of increased mortality: Confusion, Urea, Respiratory rate, low Blood pressure, and age 65 or greater. Lim et al[20] suggested that patients with a CURB-65 score of 2 be treated as inpatients; those with a score of 3 or greater will often require an ICU.* These prognostic tools do not take into account the psychosocial factors and other comorbidities that

*Confusion based on specific mental test or disorientation to person, place, or time, Urea >7 mmol/L (20 mg/dL), Respiratory Rate ≥30 breaths/min, Blood pressure systolic <90 mm Hg or diastolic ≤60 mm Hg, and age ≥65 years.

may also play a role in the emergency physician's determination of the best site of treatment for patients with CAP.

Most patients admitted for CAP are first cared for in the ED.[21] This clinical policy critically evaluates the available evidence about 2 often controversial critical issues in the care of patients admitted with the diagnosis of CAP.[11,13,22-25] The focused critical questions addressed in this policy include the following:

1. Are routine blood cultures indicated in patients admitted with CAP?
2. In adult patients with CAP without severe sepsis, is there a benefit in mortality and morbidity from the administration of antibiotics within a specific time course?

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature. Multiple searches of MEDLINE, MEDLINE In-Process, and the Cochrane database were performed. Specific key words/phrases used in the searches are identified under each critical question. All searches were limited to English-language sources, human studies, and adults. Additional articles were reviewed from the bibliography of articles cited and from published textbooks and review articles. Subcommittee members supplied articles from their own files, and more recent articles identified during the process were also included.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.[26] This policy is a product of the American College of Emergency Physicians (ACEP) clinical policy development process, including expert review, and is based on the existing literature; when literature was not available, consensus of emergency physicians was used. Expert review comments were received from individual emergency physicians and from individual members of the American College of Chest Physicians, the American College of Physicians, the Infectious Diseases Society of America, the Institute for Clinical Systems Improvement, the Society for Academic Emergency Medicine, and ACEP's Section on Critical Care Medicine. Their responses were used to further refine and enhance this policy; however, their responses do not imply endorsement of this clinical policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly.

All articles used in the formulation of this clinical policy were graded by at least 2 subcommittee members for strength of evidence and classified by the subcommittee members into 3 classes of evidence on the basis of the design of the study, with design 1 representing the strongest evidence and design 3 representing the weakest evidence for therapeutic, diagnostic, and prognostic clinical reports, respectively (Appendix A). Articles were then graded on 6 dimensions thought to be most relevant to the development of a clinical guideline: blinded versus nonblinded outcome assessment, blinded or randomized allocation, direct or indirect outcome measures (reliability and validity), biases (eg, selection, detection, transfer), external validity (ie, generalizability), and sufficient sample size. Articles received a final grade (Class I, II, III) on the basis of a predetermined formula, taking into account design and quality of study (Appendix B). Articles with fatal flaws were given an "X" grade and not used in formulating recommendations in this policy. Evidence grading was done with respect to the specific data being extracted and the specific critical question being reviewed. Thus, the level of evidence for any one study may vary according to the question, and it is possible for a single article to receive different levels of grading as different critical questions are answered. Question-specific level of evidence grading may be found in the Evidentiary Table included at the end of this policy.

Clinical findings and strength of recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on strength of evidence Class I or overwhelming evidence from strength of evidence Class II studies that directly address all of the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on strength of evidence Class II studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of strength of evidence Class III studies).

Level C recommendations. Other strategies for patient management that are based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, strength of prior beliefs, and publication bias, among others, might lead to such a downgrading of recommendations.

This policy is not intended to be a complete manual on the evaluation and management of adult patients with CAP but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain enough quality information to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the emergency physician should consider. ACEP clearly recognizes

the importance of the individual physician's judgment. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the crucial questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in hospital-based EDs.

Inclusion Criteria. This guideline is intended for patients 18 years of age or older with signs and symptoms of CAP and radiographic evidence of pneumonia.

Exclusion Criteria. This guideline is not intended for patients who are pregnant, or immunocompromised (including patients with HIV/AIDS, organ transplant, or recipients of corticosteroids, antineoplastic therapy, or other immunosuppressive agents), or have been hospitalized within the last 30 days.

CRITICAL QUESTIONS

1. Are routine blood cultures indicated in patients admitted with CAP?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Do not routinely obtain blood cultures in patients admitted with CAP.

Level C recommendations. Consider obtaining blood cultures in higher-risk patients admitted with CAP (eg, severe disease, immunocompromise, significant comorbidities, or other risk factors for infection with resistant organisms).

Key words/phrases for literature searches: pneumonia, community-acquired pneumonia, blood cultures, microbiology, bacteremia, utility of blood cultures, timeline 1996 – May 20, 2009.

The following have been identified as CMS core measures for patients admitted with CAP: (1) the collection of blood cultures prior to antibiotic administration, when ED blood cultures are drawn; (2) blood cultures performed within 24 hours prior to or 24 hours after hospital arrival for patients who were transferred or admitted to the ICU within 24 hours of presentation to the hospital.[9] The 2007 American Thoracic Society and Infectious Diseases Society of America guidelines for the management of patients with CAP recommended pretreatment blood cultures for those patients hospitalized with the following conditions: cavitary infiltrates, leukopenia, active alcohol abuse, chronic severe liver disease, asplenia, positive test result for pneumococcal urinary antigen, pleural effusion, or those admitted to the ICU. Blood cultures are optional for those without the specifically listed conditions.[27]

Ideally, blood cultures identify a pathogen and its susceptibility, allowing antibiotic therapy to be customized for each patient. However, blood cultures are infrequently positive, and blood culture results do not often lead to change in management. A variety of Class II and III studies have reported the incidence of positive culture results in patients admitted with CAP. The yield reported ranges from 0% in a series of 74 patients with nonsevere CAP without significant comorbidities[28] to 33% in 146 ICU patients with CAP from Reunion Island.[29] Typically, the range is 1% to 16%.[30-41]

A number of Class II and III studies have investigated the impact of blood cultures on antibiotic management in CAP patients. Antibiotic therapy was changed based on blood culture results in 0% to 5% of patients cultured.[31-33,38,39,42-44] Change in patient condition (either improvement or deterioration) was more likely to prompt antibiotic modification than results of blood cultures.[33,44,45] Few changes were made for coverage of resistant organisms identified by blood cultures. The Class II study by Campbell et al[31] found that only 0.4% of blood cultures drawn yielded an organism resistant to recommended empiric antibiotics. Similarly, the Class II study by Kennedy et al[39] noted 4 of 414 cultures drawn (1%) yielded resistant organisms, resulting in 2 patients having their initial treatment changed (2 others had coverage altered to more effective antibiotics before culture results were known). One Class II study[45] and multiple Class III studies reporting changes in empiric therapy based on blood culture results demonstrate similar findings. These studies, ranging in size from 86 to 517 patients, reported organisms resistant to empiric therapy in 0% to 2.7% of patients that were cultured.[32,33,38,42-46]

There are few data about blood culture performance in CAP patients and association with outcomes such as mortality, time to clinical stability, and length of stay. In a Class II multicenter study, Dedier et al[47] retrospectively examined 1,062 patients with a primary admission diagnosis of pneumonia. They found no difference in mortality or length of stay between patients who had blood cultures and those who did not have blood cultures before receiving antibiotics and no difference in mortality or length of stay between patients who had blood cultures and those who did not have blood cultures within 24 hours of admission. In the frequently cited Class III study by Meehan et al,[48] investigators retrospectively examined a national study set of 1,343 Medicare patients with a discharge diagnosis of pneumonia. The authors concluded that blood culture collection within 24 hours was associated with lower 30-day mortality; however, the odds ratio (OR) was 0.9, with a confidence interval (CI) of 0.81 to 1.0 and a nonsignificant P value of 0.07. This same study examined collection of blood cultures before or after antibiotic administration and found no significant association with lower mortality if patients had blood cultures collected before receiving antibiotics.

Blood culture results may be misleading and may cause unintended consequences. False-positive or contaminated specimens are common, and in some studies, rates of false-positive blood cultures approach those of true-positive.[32,33,39-40,42] Treatment based on preliminary false-positive blood culture results may lead to unnecessary antibiotic coverage and increased length of stay, pending final identification of the organism. Metersky et al[40] retrospectively analyzed 13,043 Medicare patients with CAP and found 7% with true-positive blood cultures and 5% false-positive blood cultures. Patients

with contaminated blood cultures had an average length of stay of 1 day longer than those who did not have contaminated blood cultures ($P<0.01$). False-positive blood cultures are also costly. Bates et al[49] reported that total hospital charges were $4,000 greater for patients with contaminated blood cultures compared with those with negative blood cultures.

Data suggest that blood cultures are more likely to provide results leading to a change in management in select patients. Liver disease, hypotension, hypothermia or fever, tachycardia, uremia, hyponatremia, and leucopenia or leukocytosis have been identified as independent predictors of bacteremia.[40] Immunocompromised patients and patients from nursing homes or other long-term care facilities are more likely to have unusual or resistant pathogens identified by blood cultures.[34,39,50] Patients with severe pneumonia may also benefit from blood culture tests.[29,51] In a prospective Class III study of 209 patients, Waterer and Wunderink[38] found that blood culture results led to change in antibiotics only in patients with PSI class IV and V disease, whereas patients in PSI class I to III had no antibiotic changes based on blood culture results.

In summary, the routine use of blood cultures in all patients admitted with CAP has a low yield and rarely leads to change in management or outcome for patients admitted with CAP. False-positive blood culture results may complicate the course for patients admitted with CAP. Therefore, blood cultures should be tailored to the individual patient. Patients with severe pneumonia, who are immunocompromised or have other significant comorbidities, may benefit from having blood cultures drawn. Because antibiotic administration before blood culture testing decreases blood culture yield, when blood cultures are necessary, they should be drawn before antibiotic administration.[37,40,41]

2. In adult patients with CAP without severe sepsis, is there a benefit in mortality or morbidity from the administration of antibiotics within a specific time course?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. There is insufficient evidence to establish a benefit in mortality or morbidity from antibiotics administered in less than 4, 6, or 8 hours from ED arrival.

Level C recommendations. Administer antibiotics as soon as feasible once the diagnosis of CAP is established; there is insufficient evidence to establish a benefit in morbidity or mortality from antibiotics administered within any specific time course.

Key words/phrases for literature searches: pneumonia, community-acquired pneumonia, time to treatment, rapid antibiotic delivery, morbidity, mortality, outcomes, length of stay, quality of care, timeline 1988 – May 20, 2009.

The timely administration of antibiotics to infected patients is good emergency medical practice. Before giving antibiotics, a reasonable assurance of the diagnosis is essential to avoid mistreatment, medication overuse, and increased antibiotic resistance.[13,22,52]

In the most recent consensus guidelines on the management of CAP in adults, the Infectious Diseases Society of America and the American Thoracic Society agreed that there is a paucity of data to support a specific time recommendation for the administration of antibiotics in ED patients with CAP.[27] Their recommendation states: *for patients admitted through the ED, the first antibiotic dose should be administered while* [the patient is] *still in the ED.*[†]

Four-Hour Cutoff

In a frequently cited article, Houck et al[53] analyzed whether the time to first antibiotic dose might be associated with reductions in mortality and morbidity. In a retrospective multicenter, Class III study, Houck et al[53] examined the charts of 13,771 Medicare patients with a primary or secondary International Classification of Diseases, Ninth Revision (ICD-9) diagnosis of pneumonia, who had not received out-of-hospital antibiotics. The patients analyzed were older than 65 years, had not received out-of-hospital antibiotics, and had radiographic evidence of pneumonia in the ED. This study showed an association between antibiotics administered within 4 hours and a decreased 30-day mortality, with an OR of 0.85 (95% CI 0.76 to 0.95). There was also a significant association with reduction of inhospital mortality and reduction of length of stay exceeding the 5-day median.

This study's limitations include the following: more patients in the group with time to first antibiotic dose less than 4 hours received appropriate antibiotics, though this was included in multivariate analysis.[53] There was a post hoc determination of the 4-hour cutoff. Any of the cutoff times from 3 to 8 hours were associated with similar 30-day mortality. The researchers chose the 4-hour cutoff, even though adjusted ORs of the 4- and 8-hour cutoffs were identical. They attempted to control for confounders through the performance of multivariate analysis. Although the study controlled for many possible confounders, the possibility of missing others potentially biases the results, which may account for the fact that despite the multivariate analysis, patients who received antibiotics between 0 and 2 hours did not have any significant mortality reduction.

Early administration of antibiotics is reliant on the early diagnosis of pneumonia. Patients whose disease is more difficult to diagnose because of atypical presentations may receive their antibiotics later. If any of the factors that lead to the delayed diagnosis are also associated with mortality, then the link between early antibiotic administration and mortality may be spurious. Waterer et al[54] examined these factors in a prospective Class II study. The researchers performed an observational study of time to first antibiotic dose in patients older than 18 years and diagnosed with CAP during their hospitalization. In univariate analysis, this study confirmed the aforementioned association between time to first antibiotic dose less than 4 hours and mortality. However, when the data were examined for factors that can cause a delayed

[†]Infectious Diseases Society of America/American Thoracic Society grading: moderate recommendation, level III evidence.

diagnosis of pneumonia, 3 factors emerged: altered mental status, the absence of hypoxia, and the absence of fever. When reanalyzed controlling for these factors, all of the mortality benefit associated with time to first antibiotic dose less than 4 hours disappeared. Altered mental status and the absence of fever remained associated with increased mortality after the multivariate analysis. This study's results indicate that for patients presenting with CAP and altered mental status or the inability to mount a febrile response, it may be more difficult to rapidly diagnose pneumonia, and they may be at higher risk for death.[54] The study by Houck et al[53] did not specifically control for altered mental status or the presence of fever in the multivariate analysis.

In a prospective, observational Class II study, Silber et al[55] examined the differences in *time to clinical stability*[‡] in 409 patients based on their door-to-antibiotic time. Three cohorts were analyzed: antibiotics in less than 4 hours, antibiotics in 4 to 8 hours, and antibiotics in greater than 8 hours. There were no statistically significant differences in time to clinical stability between the groups.

In another Class II study, Marrie and Wu[56] implemented a CAP pathway for non-ICU patients at 6 Canadian hospitals. They prospectively analyzed the effects of time to first antibiotic dose on inhospital mortality. Of the 3,043 patients included in analysis, the mortality rate for time to first antibiotic dose less than 4 hours was 9.2% and the rate for time to first antibiotic dose greater than 4 hours was 8.6%. If patients who received antibiotics before their arrival at the ED were removed (as in the study by Houck et al[53]), the mortality rate for time to first antibiotic dose less than 4 hours was 8.3% and the mortality rate for time to first antibiotic dose greater than 4 hours was 8.1%, a nonsignificant difference.

Battleman et al[57] performed a Class III, multicenter, retrospective analysis of 609 patients with a chart-coding diagnosis of pneumonia. They examined the association between time to first antibiotic dose and prolonged length of stay (prolonged length of stay was defined as ≥9 days). They found an association between shorter time to first antibiotic dose and fewer patients with prolonged length of stay. This finding was also observed in patients who received their antibiotics in the ED rather than on the floor. This study excluded patients who died, and the actual data analysis of prolonged length of stay was not provided. Potential factors that may lead to a delayed diagnosis were not included in the analysis.

Six-Hour Cutoff

No research has specifically examined a 6-hour cutoff for the time to first antibiotic dose. This time period was part of the data of the study by Houck et al[53] mentioned above. This cutoff had a significant association with reduced mortality (adjusted OR 0.84; 95% CI 0.73 to 0.95); but the conclusions are limited by all of the same factors present in the 4-hour cutoff.

Beyond 6 Hours

An 8-hour cutoff for time to first antibiotic dose has been analyzed in a number of studies. A large, multicenter, retrospective, Class III study by Meehan et al[48] demonstrated an association between antibiotic administration within 8 hours of ED arrival and mortality (adjusted OR 0.85; 95% CI 0.75 to 0.96). This study shares the same methodology as the analysis by Houck et al,[53] and its conclusions are limited by many of the same issues. Patients were included based on claims data, which may have led to selection bias. Confounding factors such as altered mental status, the absence of fever, and other clinical factors hindering diagnosis were not included in the multivariate analysis.

The study by Marrie and Wu[56] mentioned above also included data on time to first antibiotic dose less than 8 hours compared with greater than 8 hours. There was no significant mortality difference between these 2 groups. Even when patients who received antibiotics before arrival at the hospital were removed from the cohorts, no significant mortality benefit emerged for early antibiotic administration.[§]

Dedier et al[47] retrospectively studied 1,062 CAP patients from 38 hospitals. This Class III study examined the effect of time to first antibiotic dose less than 8 hours on inpatient mortality, length of stay, and time to clinical stability. There were no significant associations with rapid antibiotic administration in any of these measures. There is insufficient evidence to establish a specific cutoff time for antibiotics administration in patients who are diagnosed with CAP in the ED. In the noncritically ill patient, it is prudent to administer antibiotics as soon as possible after a definitive diagnosis is made.

Relevant industry relationships of subcommittee members: There were no relevant industry relationships disclosed by the subcommittee members.

Relevant industry relationships are those relationships with companies associated with products or services that significantly impact the specific aspect of disease addressed in the critical question.

Earn CME Credit: Continuing Medical Education is available for this article at: http://www.ACEP.EMedHome.com.

REFERENCES

1. Arias E, Smith BL. Deaths: preliminary data for 2001. *Natl Vital Stat Rep*. 2003;51:1-44.
2. Centers for Medicare and Medicaid Services. Medicare and Medicaid statistical supplement, 1995. *Healthcare Finance Rev Stat*. Suppl 1995; 1–388.
3. Halm EA, Tierstein AS. Clinical practice. Management of community-acquired pneumonia. *N Engl J Med*. 2002;347:2039-2045.

[‡]Time to clinical stability is a composite measure of the first 24-hour period during which the patient has all of the following: systolic blood pressure ≥90 mm Hg, pulse rate ≤100 beats/min, respiratory rate ≤24 breaths/min, temperature ≤101°F, O_2 saturation ≥90, and the ability to eat.

[§]*P* values of 0.81 were calculated from the study data with the SPSS 14.0 statistical package (SPSS, Inc, Chicago, IL).

4. Feikin DR, Schuchat A, Kolczak M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995-1997. *Am J Public Health*. 2000;90:223-229.
5. Talan PA, DeBleuix P, Kollef MH. A new paradigm in emergency medicine: healthcare-associated pneumonia. *Clinical Courier*. 2007;25:1-16.
6. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171:388-416.
7. Kollef MH, Shorr A, Tabak YP, et al. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest*. 2005;128:3854-3862.
8. Hiramatsu K, Niederman MS. Health-care-associated pneumonia: a new therapeutic paradigm. *Chest*. 2005;128:3784-3787.
9. The Joint Commission. Specifications manual for national hospital quality measures. Available at: http://www.jointcommission.org/PerformanceMeasurement/PerformanceMeasurement/Current+NHQM+Manual.htm. Accessed May 15, 2009.
10. Pines JM, Hollander JE, Lee H, et al. Emergency department operational changes in response to pay-for-performance and antibiotic timing in pneumonia. *Acad Emerg Med*. 2007;14:545-548.
11. Kanwar M, Brar N, Khatib R, et al. Misdiagnosis of community-acquired pneumonia and inappropriate utilization of antibiotics: side effects of the 4-h antibiotic administration rule. *Chest*. 2007;131:1865-1869.
12. Khalil A, Kelen G, Rothman RE. A simple screening tool for identification of community-acquired pneumonia in an inner city emergency department. *Emerg Med J*. 2007;24:336-338.
13. Metersky ML, Sweeney TA, Getzow MB, et al. Antibiotic timing and diagnostic uncertainty in Medicare patients with pneumonia. Is it reasonable to expect all patients to receive antibiotics within 4 hours? *Chest*. 2006;130:16-21.
14. Fee C, Weber EJ, Maak CA, et al. Effect of emergency department crowding on time to antibiotics in patients admitted with community-acquired pneumonia. *Ann Emerg Med*. 2007;50:501-509.
15. Pines JM, Localio AR, Hollander JE, et al. The impact of emergency department crowding measures on time to antibiotics for patients with community-acquired pneumonia. *Ann Emerg Med*. 2007;50:510-516.
16. Pines JM, Hollander JE, Localio AR, et al. The association between emergency department crowding and hospital performance on antibiotic timing for pneumonia and percutaneous intervention for myocardial infarction. *Acad Emerg Med*. 2006;13:873-878.
17. Capelastegui A, Espana PP, Quintana JM, et al. Validation of a predictive rule for the management of community-acquired pneumonia. *Eur Respir J*. 2006;27:151-157.
18. Aujesky D, Auble TE, Yealy DM, et al. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. *Am J Med*. 2005;118:384-392.
19. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243-250.
20. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377-382.
21. Yealy DM, Auble TE, Stone RA, et al. The emergency department community-acquired pneumonia trial: methodology of a quality improvement intervention. *Ann Emerg Med*. 2004;43:770-782.
22. Walls RM, Resnick J. The Joint Commission on Accreditation of Healthcare Organizations and Center for Medicare and Medicaid Services community-acquired pneumonia initiative: what went wrong? *Ann Emerg Med*. 2005;46:409-411.
23. Fee C, Sharpe BA, Nguy M, et al. JCAHO/CMS core measures for community-acquired pneumonia. *Ann Emerg Med*. 2006;47:505-506.
24. Moran GJ, Abrahamian FM. Blood cultures for community-acquired pneumonia: can we hit the target without a shotgun? *Ann Emerg Med*. 2005;46:407-408.
25. Rothman RE, Quianzon CCL, Kelen GD. Narrowing in on JCAHO recommendations for community-acquired pneumonia. *Acad Emerg Med*. 2006;13:983-985.
26. Schriger DL, Cantrill SV, Greene CS. The origins, benefits, harms, and implications of emergency medicine clinical policies. *Ann Emerg Med*. 1993;22:597-602.
27. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44:S27-S72.
28. Theerthakarai R, El-Halees W, Ismail M, et al. Nonvalue of the initial microbiological studies in the management of nonsevere community-acquired pneumonia. *Chest*. 2001;119:181-184.
29. Paganin F, Lilienthal, F, Bourdin A, et al. Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor. *Eur Respir J*. 2004;24:779-785.
30. Beovic B, Bonac, B, Kese D, et al. Aetiology and clinical presentation of mild community-acquired bacterial pneumonia. *Eur J Clin Microbiol Infect Dis*. 2003;22:584-591.
31. Campbell SG, Marrie TJ, Anstey R, et al. The contribution of blood cultures to the clinical management of adult patients admitted to the hospital with community-acquired pneumonia: a prospective observational study. *Chest*. 2003;123:1142-1150.
32. Chalasani NP, Valdecanas MA, Gopal AK, et al. Clinical utility of blood cultures in adult patients with community-acquired pneumonia without defined underlying risks. *Chest*. 1995;108:932-936.
33. Corbo J, Friedman B, Bijur P, et al. Limited usefulness of initial blood cultures in community acquired pneumonia. *Emerg Med J*. 2004;21:446-448.
34. El-Solh AA, Sikka P, Ramadan F, et al. Etiology of severe pneumonia in the very elderly. *Am J Respir Crit Care Med*. 2001;163:645-651.
35. Ewig S, Bauer T, Hasper E, et al. Value of routine microbial investigation in community-acquired pneumonia treated in a tertiary care center. *Respiration*. 1996;63:164-169.
36. Fine MJ, Stone RA, Singer DE, et al. Processes and outcomes of care for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team (PORT) cohort study. *Arch Intern Med*. 1999;159:970-980.
37. Glerant JC, Hellmuth D, Schmit JL, et al. Utility of blood cultures in community-acquired pneumonia requiring hospitalization: influence of antibiotic treatment before admission. *Respir Med*. 1999;93:208-212.
38. Waterer GW, Wunderink RG. The influence of the severity of community-acquired pneumonia on the usefulness of blood cultures. *Respir Med*. 2001;95:78-82.
39. Kennedy M, Bates DW, Wright SB, et al. Do emergency department blood cultures change practice in patients with pneumonia? *Ann Emerg Med*. 2005;46:393-400.
40. Metersky ML, Ma A, Bratzler DW, et al. Predicting bacteremia in patients with community-acquired pneumonia. *Am J Respir Crit Care Med*. 2004;169:342-347.
41. van der Eerden MM, Vlaspolder F, de Graaff CS, et al. Value of intensive diagnostic microbiological investigation in low- and high-

risk patients with community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis*. 2005;24:241-249.
42. Ramanujam P, Rathlev NK. Blood cultures do not change management in hospitalized patients with community-acquired pneumonia. *Acad Emerg Med*. 2006;13:740-745.
43. Socan M, Marinic-Fiser N, Kraigher A, et al. Microbial aetiology of community-acquired pneumonia in hospitalized patients. *Eur J Clin Microbiol Infect Dis*. 1999;18:777-782.
44. Woodhead MA, Arrowsmith J, Chamberlain-Webber R, et al. The value of routine microbial investigation in community-acquired pneumonia. *Respir Med*. 1991;85:313-317.
45. Sanyal S, Smith PR, Saha AC, et al. Initial microbiologic studies did not affect outcome in adults hospitalized with community-acquired pneumonia. *Am J Respir Crit Care Med*. 1999;160:346-348.
46. Waterer GW, Jennings SG, Wunderink RG. The impact of blood cultures on antibiotic therapy in pneumococcal pneumonia. *Chest*. 1999;116:1278-1281.
47. Dedier J, Singer DE, Chang Y, et al. Processes of care, illness severity, and outcomes in the management of community-acquired pneumonia at academic hospitals. *Arch Intern Med*. 2001;161:2099-2104.
48. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA*. 1997;278:2080-2084.
49. Bates DW, Goldman L, Lee TH. Contaminant blood cultures and resource utilization. The true consequences of false-positive results. *JAMA*. 1991;265:365-369.
50. Lujan M, Gallego M, Fontanals D, et al. Prospective observational study of bacteremic pneumococcal pneumonia: effect of discordant therapy on mortality. *Crit Care Med*. 2004;32:625-631.
51. Moine P, Vercken JB, Chevret S, et al. Severe community-acquired pneumonia. Etiology, epidemiology, and prognosis factors. French Study Group for Community-Acquired Pneumonia in the Intensive Care Unit. *Chest*. 1994;105:1487-1495.
52. Houck PM. Antibiotics and pneumonia: is timing everything or just a cause of more problems? *Chest*. 2006;130:1-3.
53. Houck PM, Bratzler DW, Nsa W, et al. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med*. 2004;164:637-644.
54. Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. *Chest*. 2006;130:11-15.
55. Silber SH, Garrett C, Singh R, et al. Early administration of antibiotics does not shorten time to clinical stability in patients with moderate-to-severe community-acquired pneumonia. *Chest*. 2003;124:1798-1804.
56. Marrie TJ, Wu L. Factors influencing in-hospital mortality in community-acquired pneumonia: a prospective study of patients not initially admitted to the ICU. *Chest*. 2005;127:1260-1270.
57. Battleman DS, Callahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia: link between quality of care and resource utilization. *Arch Intern Med*. 2002;162:682-688.

Evidentiary Table.

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Theerthakarai et al[28]	2001	Prospective observational study; 1 hospital in Paterson, NJ	Enrolled consecutive patients with the diagnosis of CAP to assess the value of the initial microbiological studies, consisting of sputum Gram's stain, sputum culture, and blood culture, in the etiologic diagnosis of CAP without comorbidity	212 patients screened,74 patients included; ages 22-64 y; all patients had: sputum Gram's stain (all mixed flora), sputum culture (4 pathogens 5%), blood cultures (all negative)	No positive blood culture results in this low-risk population with nonsevere CAP; all patients had improved symptoms by 48 h and became afebrile in 96 h; no patient required a change in empiric antibiotic coverage instituted at admission	Small sample size; unusually low yield on cultures; no baseline patient comparisons; study included only those patients able to produce valid sputum sample, they could differ from all patients with CAP; possible selection bias; 21 (28%) did not meet ATS guideline criteria for admission; multiple exclusion criteria, essentially eliminating all high-risk, elderly, and sick patients	III
Paganin et al[29]	2004	Prospective observational study 1995-2004; data from 1 hospital on a French island in the Indian Ocean	Consecutive patients admitted from the ED to ICU for CAP from 9/1995-12/2000; study objective: to assess the etiology and prognostic factors of CAP patients admitted to the ICU; exclusion criteria: severe immunosuppression	146 patients, 34 excluded as they did not meet definition of CAP; 112 total included; 94 (84%) male, 70 (62.5%) alcoholic, 48 (43%) died; 55 patients PSI I-II-III; 57 patients PSI IV-V; all had at least 1 blood culture; 37 (33%) positive blood culture; 23 *S pneumoniae*, 9 *Klebsiella*, 2 cases of resistant *S pneumoniae*	Blood culture more likely to be positive in sicker patients, and positive blood culture was an independent risk factor for death in sicker patients with CAP (relative risk 2.7; CI 0.8-8.9; *P*=0.0002), also septic shock, high SAPS II score and infection with *Klebsiella*	Study setting and population (French island in the Indian Ocean), mostly male, mostly alcoholic; not generalizable, selection bias; low level of antibiotic resistance; 55 patients PSI I-II-III (why were these in the ICU?)	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Beovic et al[30]	2003	Prospective; multicenter in Slovenia	Consecutive patients with CAP presenting to 7 study centers looking at etiology and clinical picture of mild CAP; study patients were both inpatient and outpatients	116 patients enrolled, 113 included in study 109 had complete data; 96/109 (88%) were PSI I or II; 1 patient had a positive blood culture (*S pneumoniae*); etiology established in 68 (62.4%), 17 typical, 42 atypical, 9 mixed	Atypical pathogens play an important role in mild CAP; there was a substantial similarity in the clinical presentation of pneumonia caused by different agents; blood cultures are very rarely positive in mild CAP treated with oral antibiotics	Treatment with oral agents was inclusion criteria; potential selection bias; very small number of patients given that enrollment included 7 study centers; study patients were both inpatient and outpatients; investigators do not report how many were inpatients	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Campbell et al[31]	2003	Prospective; multicenter, 19 centers in Canada	Patients admitted with CAP either receiving care per clinical guideline or conventional management; clinical usefulness of blood culture in the management of patients hospitalized with CAP	2,804 patients enrolled, 1,061 excluded; 716 intervention arm; 1,027 conventional arm; 760 (74%) blood cultures drawn, 43 (5.7%) "significant" positive blood culture; 3 patients (0.4%, 3/760) changed to broader spectrum as indicated by blood culture, 1 MSSA, 1 PRSP, 1 MRSA; 6 changed to broader spectrum not indicated by blood culture; 12 changed to narrower/cheaper as indicated by blood culture; 2 changed to narrower/cheaper not indicated by blood culture; 17 continued empiric therapy despite blood culture indication to step down; blood culture results did not correlate with PSI	There was a 2% chance (15/760) of having a change of therapy directed by blood culture results; in only 0.4% was this change likely to have improved the outcome for the patient; those with positive blood culture had a 39% chance of having therapy changed due to blood culture results, and a 42% chance of having therapy continued not indicated by blood culture results; routine blood cultures rarely contribute significantly to the clinical management of CAP	Data pulled from study on use of clinical pathway for managing CAP — limits internal validity; large number of patients excluded — potential selection bias; intervention arm patients may be less likely to step down or change drugs because drug is supplied; intervention patients more likely to have blood culture drawn (58% vs. 33%); limits validity; baseline characteristics of patients not compared; selection bias; false-positive contaminants not counted or discussed	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Chalasani et al[32]	1995	Retrospective; single institution	Chart review of adults hospitalized with CAP to determine the clinical utility of obtaining routine blood culture before the administration of antibiotics in certain non-immunosuppressed patients	1,250 patients identified with discharge diagnosis of CAP, 517 patients met study criteria; 6.6% (34) true-positive blood culture, 4.8% (25) contaminated blood culture; 56 patients had antibiotics changed: 42 patients with negative blood culture and 14 patients with positive blood culture; 1.4% (7 of 517 patients) had antibiotic change as a result of blood culture results, 6 narrowed, and 1 broadened to cover *H influenzae*	Blood cultures have limited clinical utility and questionable cost-effectiveness; no penicillin resistance noted; rate of true-positive blood culture similar to rate of contaminated blood culture	Retrospective design; patients identified by discharge diagnosis; selection bias; low rate of antibiotic resistance compared to current 2007 rates; contaminant determined by treating physician; reason for antibiotic change inferred for the chart, not necessarily documented	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Corbo et al[33]	2004	Retrospective; single institution in the Bronx	In ED patients hospitalized with CAP, the hypothesis that the proportion of false-positive blood cultures would exceed the proportion of true positives was tested; a secondary aim was to quantify the frequency with which antibiotic therapy was changed based on blood culture results	821 patients admitted, 355 had blood cultures; 20% positive blood cultures (70/355), 33 true-positive (9%) and 37 false-positive (10%); 238 patients had change in antibiotics; 25 true-positive changed antibiotics: 10 due to blood cultures, 10 due to clinical improvement, 1 due to worsening, 4 for other reasons; 26 false positive changed antibiotics: 6 due to blood cultures, 187/285 with negative blood cultures changed antibiotics with 2 changes due to blood culture results; overall, 18 patients (5%) had antibiotic change attributed to blood culture: 10 true-positive with antibiotic change (7 narrowed, 3 broadened [not because resistant]), 6 false positive with antibiotic change, 2 true-negative with antibiotic change; 151 (43%) had antibiotics changed due to clinical improvement and 23 (6%) with antibiotics changed due to clinical deterioration	Rate of contaminated blood cultures equaled rate of true-positive blood cultures; clinical condition is used much more frequently than blood culture to change antibiotics; no organism was identified by blood culture that was resistant to antibiotic regimen originally chosen	Retrospective design; underlying conditions stated to be similar in groups but no table provided; authors comment that length of stay is increased when antibiotic coverage is erroneously broadened to cover false-positive blood culture results but no data given; no data on mortality, length of stay; PSI not reported	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
El-Solh et al[34]	2001	Prospective cohort; 2 university hospitals in New York state	Elderly patients with CAP admitted to an ICU while receiving mechanical ventilation studied to determine the prevalence of respiratory pathogens and the effect of comorbidity and functional status on the microbial etiology of severe pneumonia in the very elderly; nursing home, as well as CAP patients, included	136 patients eligible, 104 patients enrolled, 57 from home, 47 from nursing home; in community patients the most common pathogen was *S pneumoniae*, legionella; in nursing home patients the most common pathogen was *S aureus* (MSSA 11, MRSA 3); mortality of 54.8% not different between community vs nursing home patients; mortality significantly higher in those who received inadequate antimicrobial therapy (39% vs 4%, *P*=0.007)	93 blood cultures, 15 positive (16%), more positive from nursing home than home (10 vs 5) but not statistically significant; elderly nursing home patients requiring mechanical ventilation are at risk for pathogens that are different from the usual CAP and those pathogens are potentially drug resistant	Few data on blood cultures; very specific, select population, not generalizable; physician care not standardized	III
Ewig et al[35]	1996	Retrospective; 1 hospital in Germany	CAP patients referred to a tertiary care center studied to determine the diagnostic yield of microbiological investigations and their value in directing antibiotic therapy; relationship between microbial results and association with pretreatment, severity of disease, and change in antibiotics	93 episodes in 92 patients, 32 ICU patients 22 transfers in from another institution; 20 died; 74% (69) treated with at least 1 antibiotic before admission; 50 blood cultures done, with 7 positive (14%); 52 serology with 12 definitive pathogens; 25 bronchoscopy with 1 definitive pathogen; 56 sputum culture — excluded to identify definitive pathogen	Results of microbial investigation led to antibiotic change in 9 cases; blood culture results led to antibiotic change in 0 cases; definitive pathogen identified in 8/32 (25%) severe and 11/51 (22%) nonsevere CAP; severity did not correlate with ability to identify pathogen—they did not specifically address blood culture and severity	Small study population given data from 8 y; although no baseline patient table, reported mix is atypical (male:female 62:30), also lots of transfers in, much potential bias, cannot generalize to ED population; PSI not reported	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Fine et al[36]	1999	Prospective observational; multicenter	Ambulatory and hospitalized CAP patients studied for process-of-care blood culture, other laboratory and microbiologic testing, length of stay, admit to ICU, mortality, time to return to usual activities	12,500 potential cases of CAP screened; 3,964 potential participants; 2,287 (57.7%) patients enrolled, 944 outpatients, 1,343 inpatients; 8.5% (77) of outpatients had blood culture before antibiotics, 2.6% (2) were positive; 71.2% (951) inpatients had blood culture before antibiotics, 82 (8.6%) were positive	Most patients with pneumonia have pneumonia of unknown etiology, negative blood culture; *S pneumoniae* and *H influenzae* most common pathogens identified; blood culture recommended despite low yield because of the prognostic importance of bacteremia and the potential to direct therapy against a specific pathogen	Large number of eligible patients not enrolled; enrolled patients were younger, more likely to be white, more likely to be low risk for mortality; few outpatients had blood culture done; study did not directly assess the effect of routine microbiologic testing on medical outcomes	III
Glerant et al[37]	1999	Prospective observational; 1 hospital in France	Patients hospitalized for moderate CAP (non-ICU) to compare the utility and cost benefits of blood culture in patients who had or had not received antibiotic therapy before admission	53 patients; all had blood cultures; 30 no previous antibiotic, 23 had previous antibiotic; 30 without previous antibiotics had 74 blood cultures drawn, 8 positive in 5 patients; 23 with previous antibiotics had 62 blood cultures drawn, 0 true-positive, 2 contaminants; bacteremia in patients without previous antibiotic 5/30 vs with antibiotic 0/23 $P<0.05$; all isolated organisms were susceptible to anti-biotic initially chosen	There is reduced clinical utility and cost benefit of blood cultures in patients hospitalized for moderate CAP who have received an antibiotic treatment before admission; blood cultures not likely to be positive in moderately ill hospitalized patients previously treated with antibiotics	Authors do not state how many CAP patients were missed or not enrolled; small study population; authors state coexisting illnesses similar in pretreated and not pretreated groups; however, no table or statistics provided to show baseline characteristics of the 2 groups; PSI not reported	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Waterer and Wunderink[38]	2001	Prospective cohort; 1 hospital in Memphis	Prospectively studied the yield and effect of blood culture in patients admitted with CAP; studied the relationship between blood culture yield and correlation with PSI, as well as whether blood culture results led to a change in management; hypothesized that blood culture would only have a significant effect on patient management in patients in PSI grades IV and V; included only if subjects had 2 blood cultures before any antibiotic; exclusion criteria: nonambulatory nursing home patients, had chemotherapy in past 30 days, had previous hospitalization in past 30 days, AIDS, immunosuppressant therapy	Higher PSI correlated with higher yield from blood culture *P*=0.02 PSI #+blood culture I – 1 (5.3%) II – 6 (10.2%) III – 4 (10.3%) IV – 10 (26.7%) V – 8 (13.9%); change in management based on blood culture results; no difference in mortality in patients with empiric antibiotic change (16%) vs those with change based on microbiological results (25%) (significance not reported); 20 *S pneumonia* isolated, 3 had MIC≥2 for penicillin, 11 resistant to erythromycin	209 subjects; all had blood cultures; 22 (10.5%) died, 38 (18.2%) positive blood culture, 9 (4%) contaminants, 29 (13.9%) true-positive blood culture, 12/29 had change in management based on blood culture results: in 7 antibiotic therapy was intensified, changed in 1 patient, and decreased in 5 patients; for PSI I-III, 11/117 had positive blood culture, 0 had change in management based on blood culture; for PSI IV-V, 18/92 had positive blood culture, 12 had change in management based on blood culture; blood culture isolate resistant to empiric antibiotic in 1 case; blood culture results led to a change in management only in sicker patients with PSI IV-V .	Prospective cohort, not clear that this was consecutive patients; only included patients who had 2 blood cultures before antibiotics; authors do not report how many total patients with CAP were admitted and did not have blood culture; also authors do not report number of patients with CAP not enrolled; potential selection bias; conclusions about patients with positive blood culture are limited by the small number of these patients, n=29; the 1 patient with a blood culture showing a resistant organism leading to a change in antibiotic died	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Kennedy et al[39]	2005	Prospective observational; 1 hospital in Boston	Patients admitted with blood culture done and CAP diagnosed, and the relationship between blood culture results and change in empiric therapy in blood culture–positive patients	3,762 ED patients had blood cultures, 414 patients diagnosed with pneumonia; 7% (29) blood cultures true-positive, 360 blood cultures negative; 6% blood cultures considered contaminated; 3 patients died before blood culture results; 15 patients had therapy altered by blood culture results: 11 narrowed, 4 broadened; in 11 patients the therapy unchanged, and of these, 8 could have been narrowed; 4 patients had blood cultures positive for organism resistant to empiric therapy; 2 had therapy changed to better antibiotic before blood culture results (based on clinical condition); all 4 of these patients had risk factors for resistant organisms: 3 nursing home residents and 1 alcoholic with multiple comorbidities; 30 organisms identified in 29 patients; 12/30 nonsusceptible to at least 1 antibiotic; 9/30 nonsusceptible to agents in more than 1 antibiotic class	Blood cultures are low yield and infrequently change management; 3.6% of all patients had blood culture; in blood culture positive patients, blood culture leads to change in management in 52% (15/29); 100 blood cultures would have to be done in CAP patients to identify 1 patient with a resistant organism; all patients with blood cultures positive for resistant pathogens had risk factors for resistant organisms: 3 nursing home residents and 1 alcoholic with multiple comorbidities; rate of true-positive blood cultures similar to rate of contaminated blood cultures	Analysis of blood culture-positive patients as a group is problematic because there are only 29 patients; low rate of penicillin resistance (20%); obtaining blood culture was part of study inclusion criteria; may overestimate blood culture yield; study did not include patients with CAP who did not have a blood culture done: selection bias	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Metersky et al[40]	2004	Retrospective; multicenter national study from Medicare claims database	Review of Medicare National Pneumonia Project/CMS QI program database to determine predictors of bacteremia; decision tool made and validated; derivation of rule: 4/1998-3/1999; validation of rule: 7/2000-3/2001	Derivation study; 39,242 cases of pneumonia,16,327 excluded — no blood culture; 5,180 excluded based on criteria and 4,692 excluded for missing data; 13,043 cases reviewed: 7% (886) bacteremia; 5% (643) contaminated blood cultures; multivariate analysis showed increased length of stay due to false-positive blood culture results; use of antibiotics before blood culture was negatively associated with bacteremia; independent predictors of bacteremia: liver disease, systolic BP <90 mm Hg; temperature <35° or ≥40° C; pulse ≥ 125 beats/min; blood urea nitrogen ≥30 mg/dL; sodium <130 mmol/L WBC <5,000/mm^3 or >20,000/mm^3; age, respiratory compromise not associated with bacteremia; validation study: 12,771 patients,7% (954) bacteremic; 849 bacteremic patients would be identified by decision tool, 105 missed; 583 (5%) contaminants	Patients with contaminated blood cultures had longer length of stay than those who did not $P<0.01$; use of antibiotics before blood culture was negatively associated with bacteremia; decision tool identified 88%-89% of patients with bacteremia while reducing 38% of blood cultures done; 20% mortality among patients with bacteremia would have been missed by decision rule; PSI not significantly associated with bacteremia	Patients identified from claims data with retrospective review, potential selection bias; patients age ≥65 y, potential for bias; not generalizable; tool is better at detecting pneumococcal bacteremia than other pathogens; only detected 65% of non-pneumococcal *Streptococcus* sp; a problem because one goal of blood culture is to identify unusual organisms; study not designed to analyze outcome; rule not tested prospectively	II for blood culture yield; III for other conclu-sions

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
van der Eerden et al[41]	2005	Prospective observational; 1 large hospital in the Netherlands	Evaluated the diagnostic yield of different microbiological tests in hospitalized patients with CAP	262 patients, 158 (60%), patients with identified pathogen, 40 (15%) positive blood cultures; no penicillin or macrolide resistant *S pneumoniae* identified; pretreatment with antibiotics led to lower blood culture yield: 5/66 (8%) vs 35/188 (19%), *P*=0.03; combination sputum examination with Gram's stain, culture, and pneumococcal antigen showed the highest diagnostic yield (49%), followed by urinary PCA test (20%), followed by blood culture (16%); no correlation between blood culture yield and disease severity/PSI	Investigation of sputum with Gram's stain; culture and pneumococcal antigen provided the largest yield in determining the etiology of CAP; pretreatment with antibiotics decreases blood culture yield	Total number of patients hospitalized for pneumonia and how many patients were not enrolled and not reported — potential selection bias; some baseline characteristics given but no table for comparison; low antibiotic resistance rate; not generalizable; no comment on effect of blood culture/microbiologic results on mortality or length of stay, or change in antibiotics	II for blood culture yield
Ramanujam and Rathlev[42]	2006	Retrospective observational; single hospital	Patients admitted from ED with diagnosis of CAP in which blood cultures were drawn before antibiotics; included ICU patients, excluded immunosuppressed, recently hospitalized and nursing home patients; all patients were treated with either ceftriaxone+azithromycin or levofloxacin	Number of positive blood cultures and changes in antibiotics due to blood culture results; recovery of resistant organisms and if empiric antibiotics are sufficient for patients with CAP	532 ED patients hospitalized with CAP; 289 patients enrolled;13 (4.5%) patients had true-positive blood cultures, 13 had false-positive blood cultures; organisms isolated were sensitive to empiric antibiotics in all cases; no patient required an antibiotic change due to resistance; 4 patients had change in antibiotics due to deterioration of clinical status	Retrospective design; small study population; many CAP patients did not have a blood culture — possible selection bias; small number of positive blood cultures with no resistant organisms, difficult to say whether empiric antibiotics are always appropriate	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Socan et al[43]	1999	Prospective; 1 hospital in Slovenia	Adult patients >15 y of age admitted with pneumonia (included nursing home patients) to determine the microbial etiology of pneumonia in adult patients	211 patients, 195 had blood cultures with blood cultures positive in 23 (12%); empiric therapy changed because of blood culture results in 2 (1% of all blood cultures or 9% of positive blood cultures) patients	Blood culture results do not often lead to change in therapy in this setting	Total number of patients hospitalized for pneumonia and number not enrolled not reported; potential selection bias; unusually low rate of pneumococcal pneumonia 5.7%, and low rate of antibiotic resistance; limits generalizability; one third of patients were taking antibiotic before admission to hospital	III
Woodhead et al[44]	1991	Prospective; 2 British hospitals	How microbiological investigations are used in an unselected group of adult patients with CAP, and evaluate the usefulness of the results obtained in changing antibiotic regimen; consecutive adults admitted with CAP; patients identified prospectively, charts reviewed retrospectively; excluded: patients admitted to geriatric ward, communicable disease unit, malignancy, immunosuppression	Change in antibiotic therapy due to microbiological identification of pathogens; antibiotic changes occurred in: 33 (31%) patients total; 13/28 (46%) of patients with pathogen identified (by any method); 20/78 (26%) of patients without pathogen identified; 9 (8%) patients had change because of results of microbiological tests; 18 (17%) had change because of clinical condition	122 patients identified, 106 included; 28 (26%) had causative pathogen identified; 86 (81%) had blood culture done, 9 (10%) positive; 4 (4%) had change because of blood culture results; 2 (2%) had coverage broadened because of blood culture results; blood cultures are infrequently positive and rarely change management	No information/reporting on antibiotic resistance, therefore unsure whether study has external validity; older data from Britain, limits generalizability; absolute number of patients with antibiotic changes is low, difficult to make conclusions based on 33 patients	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Sanyal et al[45]	1999	Retrospective; single hospital	Review of all adult patients with CAP discharged in 1996 treated by 1993 ATS guidelines to determine whether results of microbiologic studies led to change in antibiotics in patients who fail to respond to initial antibiotics (nonresponders); compared patients with severe and nonsevere CAP	184 patients, 94.6% (174) had blood cultures, 11% (19/174) blood cultures positive; 116 had sputum analysis, 34% (40/116) positive; no difference in rate of positive blood culture between severe CAP and nonsevere CAP (11% for each); 14% (25/184) did not respond to initial antibiotics; 6 nonsevere CAP, none had positive blood culture, changes in antibiotics made empirically; 19 severe CAP: 4 died <72 h, 13 had positive microbiologic studies, 1 had antibiotic change based on blood culture (grew MRSA); 11 patients had microbiologic studies sensitive to initial antibiotics, but antibiotics were changed empirically because of clinical deterioration; patients with bacteremia had greater mortality than nonbacteremic patients (21% vs 6.5%, $P<0.05$)	Blood culture changed management in 1 patient, 0.5% (1/174) of all blood cultures or 5% (1/19) of positive blood cultures; antibiotics changed empirically more frequently than per results of microbiologic studies (85% vs 15%; no P value reported); in nonresponders there was no difference in mortality between those in whom antibiotics were changed empirically and those with microbiologic study-guided changes	Difficult to come to conclusion about nonresponders because actual number of nonresponders (25) is low; retrospective design; patients identified by discharge diagnosis; low level of antibiotic resistance; all *S pneumoniae* isolated by blood cultures were susceptible to penicillin; all patients for whom microbiologic studies changed management came from long-term care facility	II for blood culture yield

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Waterer et al[46]	1999	Retrospective; 1 hospital in Memphis	To determine how often physicians change management based on blood culture results positive for *S pneumonia*; included patients admitted with diagnosis of CAP, blood culture drawn before antibiotics and at least 1 positive blood culture for *S pneumonia*; retrospective chart review performed	1,805 patients with CAP; 118 patients with positive blood culture for *S pneumonia*; 105 charts available; 74 patients with CAP and blood culture positive for *S pneumoniae* included in study; 15 isolates were penicillin resistant, 4 "high grade" (only one with MIC=4); 4 isolates were cephalosporin resistant, 1 high grade; 51 patients without penicillin allergy grew *S pneumoniae* susceptible to penicillin; antibiotics were changed to penicillin in only 11 of these (21.6%)	Blood culture changed management in 31 (42% of positive blood culture); antibiotic changed in 2 (2.7%) patients because of resistance; no correlation between disease severity and blood culture positivity; physicians often do not narrow therapy as indicated by blood culture results	Retrospective design; select population—study looks at admitted CAP patients with blood cultures positive for *S pneumoniae* only; resistance rate low and level of resistance low compared with 2007 rates of resistance; authors do not report how many patients with CAP had blood cultures done; therefore cannot calculate blood culture yield; furthermore, cannot calculate the overall utility of blood culture (of the total number of blood cultures done, what percentage led to a change in management?)	III
Dedier et al[47]	2001	Retrospective chart review; multicenter; 38 United States academic hospitals	CAP patients studied to determine relationship between prompt achievement of process of care markers (blood culture within 24 hours of admit, blood culture before antibiotic, antibiotic within 8 h of hospital arrival, oxygenation measurement within 24 h) and outcomes (reaching clinical stability within 48 h of hospital admission, decreased length of stay and inpatient deaths)	1,457 patients, 1,062 eligible; 89% admitted through ED; 76.2% had antibiotics within 8 h; 82.5% blood cultures by 24 h; 72.3% had blood cultures before antibiotics; 94.5% had oxygen measured by 24 h; increased severity of illness was associated with blood culture performance (P=0.009) and shorter time to antibiotics (P=0.04)	No improvement in death, length of stay for patients with blood culture before antibiotics or patients with blood cultures within 24 h; no consistent relationship between process-of-care marker achievement and improvement in the clinical outcomes	Retrospective design; patients identified by discharge diagnosis; selection bias; median number of patients from each hospital 28, which seems low; large number of patients excluded; high number of low-risk patients in the study population (29% PSI I-II); data not given explicitly for PSI IV-V patients; no propensity matching performed despite low rate of outcome	II for blood culture; III for anti-biotics

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Meehan et al[48]	1997	Retrospective; multicenter national study from Medicare claims database	Review of claims data from Medicare national claims history file and patient charts to assess quality of care for Medicare patients hospitalized with pneumonia and to determine whether process-of-care performance is associated with lower 30-day mortality; 4 processes of care investigated: blood cultures before antibiotics, blood cultures within 24 h, time to antibiotic administration, and oxygenation assessment within 24 h	500 potential cases were selected randomly from each state, DC, and Puerto Rico; 26,000 potential cases, 14,069 aggregate study set; 2,500 subset of sampled cases created, exclusion criteria applied to create 1,343 national study set; mean age 79.4 y; 23.4% from nursing homes; 58.2% had at least 1 comorbidity; inhospital mortality 10.3%; 30-day mortality 15.3%; blood culture collection within 24 h of admission associated with lower 30-day mortality: OR 0.9 (95% CI 0.81-1.0), *P*=0.07; blood culture collection before antibiotic administration was not significantly associated with higher or lower mortality OR 0.92 (95% CI 0.82-1.2), *P*=0.10	Administering antibiotics within 8 h of hospital arrival and collecting blood cultures within 24 hours were associated with improved survival	Retrospective review of claims data; potential selection bias; study population older, often from nursing home, often with comorbidities — patients more likely to have blood cultures anyway; Kappa for abstractors as low as 0.48 for recent chemotherapy, 0.52 for mental status; Kappa for blood culture 0.83 within 24 h; study population older and sicker than general ED patients; conclusion that blood culture done within 24 h is associated with reduced mortality comes from data with *P*=0.07, CI includes 1; statistically significant?	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Lujan et al[50]	2004	Prospective observational; 1 hospital in Barcelona	Patients age ≥18 y hospitalized with CAP with blood culture positive for *S pneumoniae* to evaluate the effect of discordant empirical therapy on outcome in bacteremic pneumococcal CAP; outcomes examined included 28-day mortality, use of vasoactive medications, and suppurative complications	100 consecutive patients, 29 pneumococcal isolates showed some resistance to penicillin: 17 intermediate minimum inhibitory concentrations (0.12-1 μg/mL), 12 high minimum inhibitory concentrations (>2 μg/mL); 18 nonsusceptible to macrolides, 2 nonsusceptible to cephalosporin, 27 patients immunocompromised; 10 patients had discordant therapy, 50% (5/10) patients with discordant therapy died compared with 13/90 (14%) who had concordant therapy; estimated excess mortality for initial discordant therapy was 35.6% (95% CI 3.73-67.4); only 3 of 9 patients still alive when blood culture demonstrated discordant therapy actually had therapy changed to appropriate therapy	Significant association between discordant therapy and higher morality in bacteremic patients with pneumococcal CAP; nursing home residence and immunocompromised patients were significantly associated with penicillin and macrolide resistance	Discordant pool included patients with intermediate resistance possible skewing results to show discordant therapy causes less harm; very small number of patients with discordant therapy (10) leads to very wide CI; specific group of patients — blood culture positive for *S pneumonia*; 6 patients receiving discordant therapy treated with amoxicillin-clavulanate as the initial empiric antibiotic, including 2 who were PSI V; not typical of empiric treatment for hospitalized patients in the United States; included immunocompromised patients — possibly biasing to higher mortality	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Moine et al[51]	1994	Prospective observational; multicenter; 15 French centers	Consecutive patients hospitalized with severe CAP in the ICU to determine causative agents, the value of clinical, biologic, and radiologic features in predicting the etiology, and to define prognostic factors in patients with severe CAP	157 CAP patients, 25 excluded; 132 study patients: 98 male, 34 female; 46 had antibiotics before admission; 127 had blood cultures, 34 (27%) positive blood cultures, 22 *S pneumoniae,* 4 *Streptococcus* species, 1 *Escherichia coli*, 5 *Klebsiella*; 31 patients had therapy modified based on bacteriologic results, 16 patients with unsuccessful treatment response had therapy modified based on bacteriologic results (changes due to blood culture in particular not reported)	27% bacteremia in this population of patients with severe CAP; blood culture yield higher in sicker patients; bacteremia significantly associated with death in this population; determining the etiology did not improve survival; 15/34 patients with positive blood culture died; bacteremia significantly associated with death (P=0.004)	Extreme male predominance 98:34; although 31 patients had therapy modified based on bacteriologic findings, it was not reported in how many blood culture specifically changed management	II
Houck et al[53]	2004	Multicenter retrospective cohort	Enrolled 18,209 patients, 4,438 patients excluded for pretreatment antibiotics; chart review of 13,771 patients ≥65 y with ICD-9 code of pneumonia from more than 3,500 hospitals who did not receive antibiotics before arrival at hospital; patients gathered during a 1-y period based on claims data	Inhospital mortality, 30-day mortality, and length of stay >5 days; as associated with antibiotic administration before or after 4 h from arrival	After performance of multivariate logistic regression, antibiotic administration within 4 h when compared to >4 h yielded an adjusted OR of 0.85 (95% CI 0.74-0.98) for inhospital mortality, an adjusted OR of 0.85 (95% CI 0.76-0.95) for 30-day mortality, and an adjusted OR of 0.9 (95% CI 0.83-0.96) for length of stay greater than 5 days	4-h cutoff was determined post hoc; 3- to 8-h cutoffs had near identical 30-day mortality associations; though included in the multivariate analysis, more patients in the antibiotics <4 h group received antibiotic regimens deemed appropriate; did not analyze for altered mental status; enrollment based on claims data and equal numbers sampled per state, not based on state population; did not analyze by individual hospital; hospitals that diagnose more efficiently may be associated with better overall care	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Waterer et al[54]	2006	Single center prospective cohort	451 patients split into antibiotic before or after 4-h groups; about 50% of patients in each cohort	Antibiotics before or after 4 h as associated with mortality; also looked at associations with severity, septic shock, hypoxia, and decreased mental status	On univariate analysis, antibiotics >4 h after arrival was associated with increased risk of death, but when multivariate analysis performed, no statistically significant increased risk of death based on antibiotic time; altered mental state associated with an adjusted OR 3.33 (95% CI 1.28-8.77) and absence of fever was associated with adjusted OR 2.55 (95% CI 1.02-6.37) for mortality	Single center; small number of mortalities in age >65 y population; no mention is made about whether any patients received out-of-hospital antibiotics	II
Silber et al[55]	2003	Prospective observational cohort	409 patients >21 y (though most >65 y) with moderate to severe pneumonia (based on PORT score) were placed into 3 groups based on their time from arrival to antibiotics (group 1 received antibiotics in <4 h, group 2 from 4 to 8 h, group 3 in >8 h)	Time to clinical stability — a composite measure of the first 24 h period that the patient has all of the following: SBP ≥90 mm Hg, pulse rate ≤100 beats/min, respiratory rate ≤24 breaths/min, temperature ≤101°F, O_2 Sat ≥90, and the ability to eat	No statistically significant differences between the groups in time to clinical stability	Excluded patients who received inappropriate antibiotics; excluded patients who never reached clinical stability; moderate sample size may have missed differences	II
Marrie and Wu[56]	2005	Multicenter, prospective observational trial	3,043 patients, mean age 70 y; excluded patients: admitted to the ICU from the ED, aspiration pneumonitis (1st y only), tuberculosis, cystic fibrosis, pregnant, or taking immunosuppressive drugs/CD4 <250	Implemented a care pathway; tracked many interventions and prognostic factors including antibiotics before or after 4 h	No significant difference in mortality with a 4 or 8 h cutoff	Only performed univariate analysis on the time to antibiotic and mortality associations; lack of multivariate analysis of confounding factors decreases clinical utility of these results	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Battleman et al[57]	2002	Multicenter retrospective cohort	609 patients from 7 hospitals with diagnosis of pneumonia based on DRG coding	Prolonged length of stay (defined as ≥9 days) as associated with door-to-needle time and whether antibiotics were administered in ED or on floor	Decreased number of patients with prolonged length of stay associated with shorter door-to-needle times and antibiotics administered in the ED	Excluded mortalities from analysis; data not shown for analysis of door-to-needle time	III

ATS, American Thoracic Society; *BP*, blood pressure; *CAP*, community-acquired pneumonia; *CI*, confidence interval; *CMS*, Centers for Medicare and Medicaid Services; *DRG*, Diagnosis-Related Group; *ED*, emergency department; *H*, *Haemophilus*; *h*, hour; *ICD-9*, International Classification of Diseases, Ninth Revision; *ICU*, intensive care unit; *MIC*, minimum inhibitory concentrations; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MSSA*, methicillin-susceptible *Staphylococcus aureus*; *min*, minute; O_2, oxygen; *OR*, odds ratio; *PCA*, pneumococcal antigen; *PORT*, Patient Outcomes Research Team; *PRSP*, penicillin resistant *Streptococcus pneumoniae*; *PSI*, pneumonia severity index; *QI*, quality improvement; *S*, streptococcus; *SAPS*, simplified acute physiology score; *Sat*, saturation; *SBP*, systolic blood pressure; *vs*, versus; *y*, year; *WBC*, white blood cell count.

Appendix A. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analyses of randomized trials	Prospective cohort using a criterion standard	Population prospective cohort
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing ≥2 interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X