Evidence Behind the 4-Hour Rule for Initiation of Antibiotic Therapy in Community-Acquired Pneumonia

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Study objective: US regulatory authorities mandate delivery of antibiotics within 4 hours of arrival for patients being admitted to the hospital with community-acquired pneumonia. This evidence-based emergency medicine review examines the scientific evidence pertaining to this requirement.

Methods: We searched MEDLINE, EMBASE, the Cochrane Library, other databases, and bibliographies. We selected articles allowing comparison of inpatient or 30-day mortality among patients receiving early versus delayed antibiotics. We prospectively categorized studies according to whether they were retrospective or prospective and whether they adjusted for severity with the Pneumonia Severity Index. We evaluated the precision with which the interval to initiation of antibiotic therapy was defined and the compliance of retrospective studies with standard reporting criteria for chart reviews.

Results: We identified 13 observational studies reporting comparative outcomes in patients receiving early versus delayed antibiotic initiation, of which 10 allowed calculation of our primary outcome. Of the 4 prospective studies, 1 allowed severity adjustment using the Pneumonia Severity Index score. Among the retrospective studies, definition of time to antibiotic therapy was frequently imprecisely defined, and compliance with standard reporting criteria for chart review was scanty in the subgroup lacking severity adjustment. Odds ratios (ORs) for mortality varied widely. One methodologically weak study reported a large benefit of early antibiotics (OR for mortality antibiotics <4 hours versus >4 hours 0.24; 95% confidence interval [CI] 0.08 to 0.71). The one study that used prospective enrollment and severity adjustment using the Pneumonia Severity Index observed a contrary result (adjusted OR for mortality, antibiotics <4 hours versus >4 hours 1.99; 95% CI 1.22 to 13.45). Results from studies reporting an 8-hour cutoff also varied in magnitude and direction of effect.

Conclusion: Evidence from observational studies fails to confirm decreased mortality with early administration of antibiotics in stable patients with community-acquired pneumonia. Although timely administration of antibiotics to patients with confirmed community-acquired pneumonia should be encouraged, an inflated sense of priority of the 4-hour time frame is not justified by the evidence. [Ann Emerg Med. 2008;51:651-662.]

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CLINICAL SCENARIO

A 54-year-old nonsmoking man with a history of diabetes presents to the emergency department (ED) with a chief complaint of productive cough with green sputum and subjective fever for 5 days. The cough was worse last night, and he could not sleep. There is no other medical history, and he takes only metformin. He has recently been transferred from another city by his employer, and although he has full insurance coverage, he has not yet located a new primary care physician. His vital signs are temperature 101.0°F (38.3°C), blood pressure 112/76 mm Hg, pulse rate 130 beats/min, respiratory rate 22 breaths/min, oxygen saturation 96% on room air, and serum glucose level 270 mg/dl. Other laboratory values, including a venous blood gas, which your staff routinely orders for patients with respiratory symptoms or fever, are close to normal. On examination, the patient appears comfortable, with no evidence of respiratory distress. Lung fields are clear, and there are no contributory physical findings. After hydration begun by the nursing staff, the pulse rate has decreased to 104 beats/min and the finger stick glucose is 180 mg/dl.

It has been a busy night in the ED, with a patient with acute myocardial infarction being prepared for the catheterization

laboratory, 2 trauma cases from the night before, and an acute stroke patient who is being given thrombolytics by the stroke team after blood pressure stabilization. Your patient with cough has been waiting almost 4 hours to be treated. You are considering your options. Several nurses and your relief are on hand, and a few suggestions are advanced. Your department has been given several warnings by administration about poor compliance with The Joint Commission's "4-hour rule" for patients with community-acquired pneumonia. One nurse suggests giving him a dose of intravenous ceftriaxone now before sending him for a chest radiograph.

You are curious about the scientific basis of the 4-hour rule and decide to look into the evidence supporting the guideline.

FORMULATING THE QUESTION

Much progress has been made in EDs in the last decade in recognizing the need to prioritize the care of patients with conditions such as ST-elevation myocardial infarction and acute ischemic stroke. In these conditions, timing is critical in determining outcome because the window for revascularization is limited.[1,2]

A few years ago, The Joint Commission and the Centers for Medicare & Medicaid Services adopted regulatory mandates pertaining to treatment of patients admitted to the hospital with community-acquired pneumonia. These include a community-acquired pneumonia core measure that antibiotic therapy be initiated within 4 hours of hospital arrival,[3] following the 2003 guidelines update on community-acquired pneumonia from the Infectious Diseases Society of America.[4] In 2007, eligible hospitals that do not submit data on the 10 core measures may receive a 2% reduction in Medicare reimbursement.[5] There is even discussion of pay for performance or differential reimbursement to physicians and hospitals, depending on how often the 4-hour rule is met. Internally, some hospitals have adopted incentive bonuses for staff who comply with various core measures.[6] We conducted an evidence-based review to determine the extent to which this 4-hour recommendation is supported by evidence from clinical research.

In considering the question posed by our scenario, we are concerned with patients who are sick enough to be admitted to the hospital. Such patients generally have a Pneumonia Severity Index corresponding to class 3 or higher according to the measure developed by the Pneumonia Patient Outcomes Research Team (PORT).[7] Patients in lower-severity classes are not generally at substantial risk for mortality or other serious clinical outcomes and are frequently treated as outpatients. On the other hand, patients with pneumonia who are critically ill or septic have a 30-day mortality risk of up to 30%[8] and might be more sensitive to the timing of antibiotics.[9]

We are primarily interested in comparing the outcomes of patients receiving antibiotics within 4 hours of presentation to those receiving antibiotics after 4 hours of presentation. The Joint Commission specification manual, although prioritizing antibiotics within 4 hours, also lists an 8-hour cutoff for antibiotic delivery, making such a comparison of important secondary interest.[3] Although current practice guidelines for treatment of community-acquired pneumonia provide for preferred antibiotic choices for patients falling into specific categories, such choices are not generally supported by randomized trial evidence and are therefore assigned relatively low grades of recommendation.[10] We therefore believe our question is best considered independently of antibiotic choice. Pneumonia patients with immunodeficiencies or receiving immunosuppressive drug regimens might also respond differently to the timing of antibiotic therapy. We therefore are restricting our inquiry to consideration of immunocompetent patients.

The literature on antibiotic timing in patients admitted with community-acquired pneumonia has addressed a number of outcomes, including mortality, morbidity, time to clinical stability, and length of hospital stay. Of these, we believe that patients who are sick enough to be admitted to the hospital for pneumonia will be most concerned about the outcome of mortality. Pneumonia patients with a PORT severity class of 3 or 4 have expected 30-day mortality rates of 1% or 9%, respectively.[8]

In view of the above considerations, we defined our question as, "In immunocompetent, moderately but non–critically ill adults being admitted from an ED to the hospital with the primary diagnosis of community-acquired pneumonia, does administration of antibiotics within 4 hours of hospital arrival decrease inhospital or 30-day mortality compared with administration later than 4 hours after hospital arrival?"

SEARCHING FOR AND SELECTING THE BEST EVIDENCE

Randomized clinical trials would ordinarily be the preferred method for determining the relative effectiveness of therapeutic alternatives.[11] However, we considered it unlikely that such trials would have been attempted because of the ethical concerns implicit in deliberately delaying initiation of antibiotic therapy to sick patients for the purposes of a study. We therefore sought both retrospective and prospective observational studies allowing the calculation of outcomes related to the timing of antibiotic therapy for patients with community-acquired pneumonia. Although our question addresses patients with moderate pneumonia severity, we wished to explore all possible sources of variability in results across otherwise relevant studies and therefore initially considered all studies involving adult immunocompetent patients with community-acquired pneumonia. We also considered studies addressing antibiotic initiation times other than 4 hours and provisionally included those whose primary outcomes were different from inhospital or 30-day mortality. We excluded studies that did not report outcome data for a control group defined by later administration of antibiotics.

On August 21, 2006, we sequentially searched MEDLINE and MEDLINE "prognosis" from 1966, EMBASE (from 1980), CINAHL (from 1982), MEDLINE In-Process & Non-Indexed Citations, and Cochrane Central Register of Controlled

Trials (CCTR) with the Ovid interface. Emergency Medical Abstracts (1977 to July 2006)[12] was also searched in August 2006 with the index terms "pneumonia," "antibiotic," and "time." We removed duplicates with each successive search. The full search strategies that were used for the large databases are reproduced in Appendices E1 and E2 (available online at http://www.annemergmed.com). We updated our MEDLINE search in August 2007 and identified no additional studies meeting our inclusion criteria.

Our search strategies included the terms "pneumonia," "community-acquired," "antibiotics," and various time-related words (eg, "time," "hours"). We screened references of articles and editorials that were relevant to our question, including those we included in our analysis. We also screened the bibliographies of relevant guidelines, including the evidence summaries cited by The Joint Commission as the basis of its regulatory guidelines[3] and the most recent update of the consensus guidelines of the Infectious Disease Society of America and the American Thoracic Society.[10] We found no randomized trials relevant to our question. Review of 5,095 hits yielded a total of 13 observational studies that fit our inclusion criteria (Figure 1).

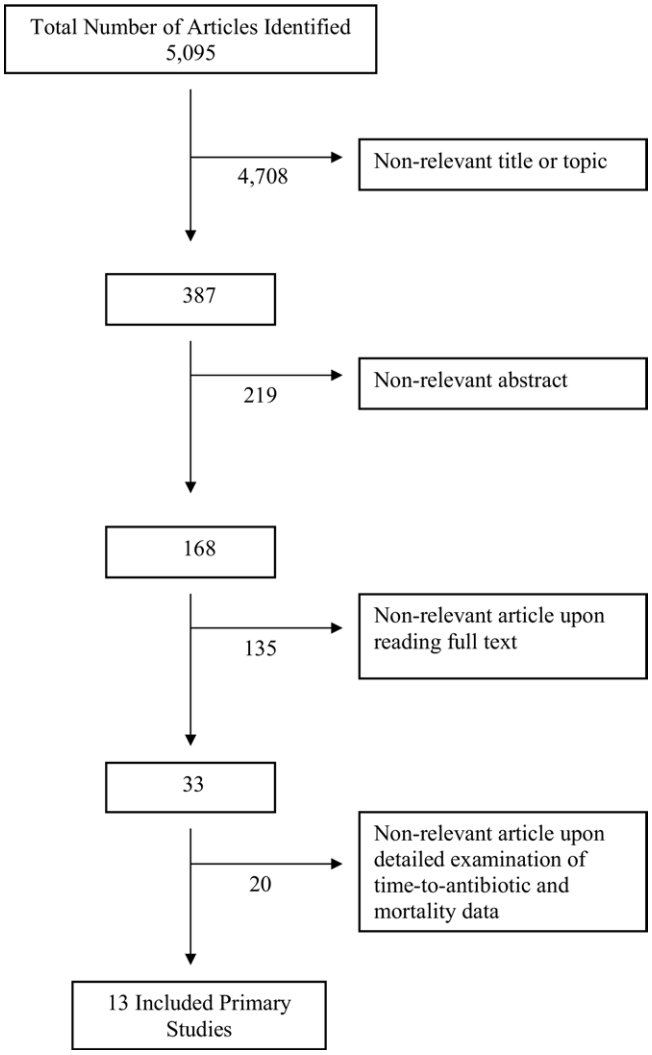

Figure 1. Process of selecting included studies (completed August 21, 2006).

ANALYZING THE EVIDENCE

Table 1 describes the 13 observational studies allowing calculation of specific outcome data in relationship to time to antibiotic therapy found in the course of our search. Because of the propensity for bias in nonrandomized studies of therapy, we prospectively decided to group the studies we found by the method of enrollment (retrospective versus prospective) and also by the use of a validated pneumonia severity score, the Pneumonia Severity Index (or PORT score),[8] for the purpose of controlling for severity. Retrospective studies of patients categorized as having pneumonia at the point they are discharged from the hospital have an important disadvantage. There may be substantial diagnostic uncertainty about the nature of these same patients' illness at the time they originally presented to an ED.[13] Lacking prospective ED-based criteria for case identification, patients receiving antibiotics later in their course might constitute more complex and more clinically ambiguous cases than those receiving them early in the course of their ED evaluation, confounding the comparison of clinical outcomes based on timing of antibiotic administration.

Similarly, patients who are sicker will tend to have worse outcomes than those who are less sick, irrespective of the timing of initiation of antibiotic therapy. Failure to control for severity will therefore likely result in false inferences about other differences in treatment. The PORT score[8] is a prospectively validated and recognized instrument[10] that has been shown to reproducibly stratify patients with community-acquired pneumonia into 5 classes corresponding to mortality risk, our own outcome of interest.[7] It was originally developed as an instrument for use in retrospective reviews,[14] and it is commonly used as a means of controlling for severity in research studies on community-acquired pneumonia.

Following these principles, we identified 4 groups of studies among those retrieved from our search: Group A, retrospective studies without controls for severity,[15-20] Group B, retrospective studies with severity controls using the PORT score,[21-23] Group C, prospective studies without severity controls,[24-26] and Group D, prospective studies with severity controls using the PORT score.[27] Each study used a specified time cutoff, most commonly 4 or 8 hours after patient arrival. Two studies were restricted to patients admitted to the ICU.[19,24] Two studied the Medicare population specifically (age 65 years and older).[22,23] Reported outcomes included length of stay and inpatient or 30-day mortality.

Because we have defined the intervention as a difference in time to administration of antibiotic therapy, measured in hours, this interval itself needs to be precisely defined for a difference in outcome to be convincingly attributed to this time difference. As summarized in Table 1, the definition of the point at which the interval defined as "time to antibiotic administration"

Table 1. Description of included studies.

Study, by First Author	Included Population	Comparisons	Outcome Measures	Design
Group A, retrospective studies without severity controls				
Rosenstein, 2000[18]	Patient Selection: 367 patients admitted through the ED and with complete data, among 684 randomly selected adults >17 years, convenience sample of 15 VHA hospitals in US in 1997, mean age not reported, CAP by DRG 89 classification for both ED and discharge diagnoses. Comorbidities/Severity: 19% admitted to ICU.	Antibiotics <2 hours vs >2 hours after ED registration time; 2-hour cutoff defined retrospectively as result of initial logistical regression analysis	Length of stay	Multicenter retrospective cohort
Lim, 2001[16]	Patient Selection: 132 patients, admitted with simple PNA (DRG 89, 90), sampled from 977 PNA patients, 85% >60 years, 4 US hospitals in 1998, excluded inpatient deaths. Comorbidities/Severity: 59% with at least 1 comorbidity (chronic lung disease, CHF, cerebrovascular disease, etc). Mortality rate in target population 1.4–3.3%.	Antibiotics <8 hours vs >8 hours after time of admission, not otherwise defined. Numerous factors considered, 8-hour cutoff not clearly prospectively defined	Length of stay. Cases and matched controls selected according to LOS >5 days vs <5 days. Patients with LOS=5 days excluded	Multicenter retrospective case control
Battleman, 2002[15]	Patient Selection: 609 adults admitted through ED with diagnosis of CAP by ED physician (DRG 89, 90), randomly selected, 7 US community and academic hospitals in 1998, mean age 67 years, 23 inpatient deaths and 4 patients who left AMA excluded. Comorbidities/Severity: 84% with COPD or other comorbid illness, 3.3% inpatient mortality.	Antibiotics in ED vs on floor. Also time from ED triage to first antibiotic administration per 8-hour interval in retrospective analysis. Average time to first antibiotics in ED 3.5 hours vs 9.5 hours on floor	Length of stay	Multicenter retrospective cohort
Ziss, 2003[20]	Patient Selection: 155 patients admitted with CAP *ICD-9* codes, confirmed for CAP, US in 1 year starting September 1999, 57 patients <18 years, 73 patients >65 years, antibiotics before hospital arrival not determined. Comorbidities/Severity: 54% with 1 comorbidity, 29% with more than 1 comorbidity (COPD, tobacco, diabetes, etc), 4.5% inpatient mortality.	Antibiotics after hospital arrival, not otherwise specified numerous factors considered, time cutoff not prospectively defined, data reported in 2-hour increments to 8 hours	Inpatient mortality, length of stay	Retrospective cohort
Mortensen, 2004[17]	Patient Selection: 420 patients admitted with CAP (or sepsis or respiratory failure and PNA), *ICD-9* codes plus CXR consistent with pneumonia and working diagnosis of pneumonia as assessed by a physician, 2 academic US hospitals in 2 years, starting January 2000, mean age 63 years, 85% men, 79% by ED, excluded patients discharged within 24 hours. Comorbidities/Severity: 32% with chronic pulmonary disease, 16% with heart failure, 16% with history of malignancy, 15% with history of CVA, 20% to ICU initially, 30-day mortality 9.8%.	Antibiotics <8 hours vs >8 hours after admission, not otherwise defined, if not by ED; 8-hour cutoff prospectively defined	30-day mortality	Multicenter retrospective cohort
Wilson, 2005[19]	Patient Selection: 96 consecutive adults admitted to ICU with severe CAP, identified by ICU databases and medical records, 2 Australian hospitals in 2.5 years, starting January 2001, mean age 59.5 years (range 21–88 years), included ward, transfers and 23% who received antibiotics before admission. Comorbidities/Severity: 83% with at least 1 comorbidity, 89% PORT class 3–5, 71% class 4–5, 73% required mechanical ventilation, 63% receiving pressors, 20% with positive blood culture, 32% mortality.	Antibiotics <4 hours vs >4 hours after ED triage time. Timing only available for 87 of 96 (90%) patients. Time cutoff not prospectively defined in protocol	ICU mortality	Multicenter retrospective cohort
Group B, retrospective studies with severity controls				
Meehan, 1997[23]	Patient Selection: 1,343 Medicare patients, mean age 74 years, pneumonia by *ICD-9* codes, randomly selected from 14,069 confirmed pneumonia diagnoses from Medicare claims, 50 US states, Washington, DC, and Puerto Rico, in 1 year starting October 1994, LOS <1 day excluded (death, discharged). Comorbidities/Severity: 58.2% with at least 1 comorbid illness (CHF, CAD, cerebrovascular disease, etc.), PSI classes 2–5, 10.3% inpatient mortality.	Antibiotics <8 hours vs >8 hours after "time of hospital arrival not otherwise specified." Blood culture timing and oxygenation also considered as process predictors. Data analyzed at 1-hour intervals	30-day mortality	Multicenter retrospective cohort

Table 1. Continued.

Study, by First Author	Included Population	Comparisons	Outcome Measures	Design
Dedier, 2001[21]	Patient Selection: 1,062 adults with CAP as discharge diagnosis, 38 US academic hospitals in 3 months starting December 1997, median age 64 years (range 18–98 years), most admitted through ED. Comorbidities/Severity: 49% with at least 1 chronic comorbid condition, all PSI classes included, 52% class 4 or 5, 6% inpatient mortality, 70% not clinically stable by 48 hours.	Antibiotics <8 hours vs >8 hours after initial nursing triage note as prospectively chosen cutoff. Prospectively defined. Blood culture timing and oxygenation also considered as process predictors	Inpatient mortality, clinical stability at 48 hours, length of stay	Multicenter retrospective cohort
Houck, 2004[22]	Patient Selection: 13,771 Medicare (>65 years) patients hospitalized with CAP (or sepsis or respiratory failure and PNA, 50 US states in 2 6-month periods in 1998 and 1998–1999, *ICD-9* codes, sampled from 39,242 PNA cases (from Medicare claims), 31% >85 years, death or discharged (LOS <1 day) excluded Comorbidities/Severity: 71% PORT class 4 or 5, 12% to ICU in first 24 hours.	Antibiotics after hospital arrival, not otherwise specified (first time documented in hospital or ED); 4-hour cutoff for antibiotics chosen only after preliminary analysis of data.	Inpatient and 30-day mortality, 30-day readmission, length of stay	Multicenter retrospective cohort
Group C, prospective studies without severity controls				
Marrie, 2005[25]	Patient Selection: 3,043 patients admitted with CAP as part of clinical pathway (not initially to ICU), 6 Canadian hospitals in 2 years starting November 2000, mean age 69.6 years. Comorbidities/Severity: 3.7% later transferred to ICU; 8.1% mortality, excluded patients admitted directly to ICU, aspiration pneumonia, tuberculosis or cystic fibrosis, immunosuppressed, prior antibiotics.	Antibiotics <4 hours vs 4-8 hours vs >8 hours after ED presentation not otherwise defined. Time cutoff not prospectively defined	Inpatient mortality (early <5 days vs late ≥5 days)	Multicenter prospective observational cohort
Bodi, 2005[24]	Patient Selection: 529 patients admitted to ICU with severe CAP, 33 Spanish hospitals in 15 months starting December 2000, mean age 59.9 years, immunocompromised included (12%), excluded nursing home, nosocomial pneumonia. Comorbidities/Severity: 37% with COPD, 24% with previous antibiotics, 66% with mechanical ventilation, 51% with shock, 28% ICU mortality.	Antibiotics <4 hours vs >4 hours after time of hospital triage. Time cutoff prospectively defined	ICU mortality	Multicenter prospective observational cohort
Waterer, 2006[26]	Patient Selection: 451 patients admitted with CAP by radiologist or critical care physician, tertiary hospital in Tennessee in 1998–2001, mean age 58.2 years, excluded immunosuppressed, nursing home. Comorbidities/Severity: 48% PSI class 3–5, 29.1% class 4-5, 8.0% inpatient mortality.	Antibiotics <4 hours vs >4 hours after ED triage time; 4-hour time cutoff prospectively defined	Inpatient mortality	Multicenter prospective observational cohort
Group D, prospective studies with severity controls				
Silber, 2003[27]	Patient Selection: 409 adults admitted with moderate to severe CAP (PORT class 3–5), US academic hospital in 9 months starting May 1999, mean age 78.4 years (range 33–101 years). Comorbidities/Severity: 68 patients (11%) inpatient mortality (analyzed separately), 50 patients (of 603) not achieving clinical stability excluded.	Antibiotics <4 hours vs 4–8 hours vs >8 hours after ED triage. Time cutoffs prospectively defined	Mortality, time to clinical stability, length of stay	Prospective observational cohort

ED, Emergency department; *VHA*, Veterans Health Administration; *CAP*, community-acquired pneumonia; *DRG*, diagnosis-related group; *ICU*, intensive care unit; *PNA*, pneumonia; *CHF*, congestive heart failure; *AMA*, against medical advice; *COPD*, chronic obstructive pulmonary disease; *ICD-9*, *International Classification of Diseases, Ninth Revision*; *CXR*, chest radiograph; *CVA*, cerebrovascular incident; *PORT*, Pneumonia Patient Outcomes Research Team; *CAD*, coronary artery disease; *LOS*, length of stay; *PSI*, pneumonia severity index (or PORT score).

started varied widely across the included studies and was poorly defined in some. Only 7 of the 13 studies reporting comparative outcomes identify time from ED triage as the point at which the time to antibiotic administration started.[15,18,19,21,24,26,27] Table 1 also illustrates that only 5 studies defined the time cutoff for antibiotic administration as part of a prospective protocol.[17,21,24,26,27]

In the 4 prospective studies,[24-27] patients were identified and enrolled once an ED diagnosis of community-acquired pneumonia was made, according to clinical signs and symptoms. To diagnose community-acquired pneumonia, Bodi et al,[24] Marrie and Wu,[25] and Waterer et al[26] (from group C) required radiographic evidence of pneumonia as part of the criteria for community-acquired pneumonia diagnosis. Silber et al[27] (from group D) relied on PORT criteria for choosing class 3 to 5 (moderate to severe) community-acquired pneumonia patients.

Table 2 addresses the quality of the 10 included studies that report mortality data. The classification of the studies into groups A through D divides the studies we considered into categories corresponding to the principal criteria used to generate the table. Table 2 therefore serves to amplify and augment the implications of these criteria. The wording of the column headers of Table 2 is intended to highlight the relationship between our methodological criteria and standard criteria for appraisal of observational studies of therapy and harm.[28] For example, in studies enrolling patients retrospectively on the basis of discharge diagnosis, those patients diagnosed with pneumonia after hospital admission would not have had the same opportunity to be treated early as those whose diagnosis was obvious to the emergency practitioners treating them. As a result, the patients treated late might constitute a different population compared with those treated early, rendering the comparison spurious.

Among studies that reported adjustment for severity, the PORT score was the most commonly used severity indicator.[8] Some studies used the Acute Physiology and Chronic Health Evaluation (APACHE) II score or miscellaneous severity indicators such as altered mental status[26] on presentation but often did not adjust mortality outcomes for severity.

As summarized in Table 2, we also examined the retrospective studies included in groups A and B with respect to published methodological criteria for chart review.[29] Group A studies were particularly deficient in reporting compliance with these criteria compared to those in group B.

Table 3 and Figure 2 summarize the mortality results of the 7 included studies that used a 4-hour cutoff for antibiotic administration. In the case of the study by Silber et al[27] (group D), data in the published report allowed the mortality rates observed in patients treated within 4 hours and in those treated later than 4 hours of ED arrival to be calculated within each of the included PORT severity classes. Using this data, we used Stata 9.0 (StataCorp, College Station, TX) software to calculate an adjusted odds ratio (OR) for mortality in patients treated in less than 4 hours compared with those treated later than 4 hours, with Mantel-Haenszel weights.

There is wide variability across the 7 studies in Table 3 with respect to the potential effect of early antibiotics compared with later antibiotics on mortality. Only 2 observed a statistically significant benefit of antibiotics within 4 hours.[19,26] Of these, the Wilson and Fergusson[19] study (group A) was restricted to patients in an ICU setting who, as we mentioned at the outset, might be particularly sensitive to the timing of antibiotic therapy. This study was methodologically weak not only by virtue of its design but also with respect to adherence to standard criteria for retrospective chart reviews. Patients who had already started receiving antibiotics before arrival to the hospital were eligible, and time to administration of the first dose of antibiotic after ED triage was available for only 90% of patients. Furthermore, the authors do not clearly state whether the 4-hour time cutoff was part of a prospective protocol or derived after data collection.

The second study, by Waterer et al[26] (group C), used well-defined time criteria and a prospectively defined time cutoff of 4 hours. We classified this study as group C because the authors did not use the validated Pneumonia Severity Index instrument as their severity control. However, the authors did report that when they used a multivariate model including altered mental status and several other variables included in the Pneumonia Severity Index instrument to adjust for severity, the trend toward lower inpatient mortality with time to antibiotic therapy less than 4 hours persisted but was no longer statistically significant (OR 0.54; 95% confidence interval [CI] 0.2 to 1.2).

Results from the study by Silber et al[27] (group D), based on our post hoc analysis, demonstrate an association between early administration of antibiotics and higher mortality (adjusted OR 1.99; 95% CI 1.22 to 13.45). The 4-hour mortality data, as summarized in Figure 2, suggest a possible relationship between study design and the direction and magnitude of observed results. The weakest studies (group A) suggest a survival benefit of early antibiotic administration for stable patients admitted to the hospital with community-acquired pneumonia. This benefit appears to diminish and finally to disappear as the design strengthens by our criteria. The Waterer et al[26] study (group C) appears to break this pattern but less so when their own adjusted analysis is considered.

Table 4 and Figure 3 summarize the effect of antibiotic timing on mortality in the 4 studies that reported an 8-hour cutoff for treatment of community-acquired pneumonia. Again, there is variability of results between studies across the respective design groups A through D. Within group B, retrospective studies using the Pneumonia Severity Index score to adjust for severity, Meehan et al[23] observed lower adjusted mortality rates in Medicare patients receiving early administration of antibiotic therapy (adjusted OR 0.85; 95% CI 0.75 to 0.96), whereas Dedier et al[21] reported a trend in the adjusted effect favoring delayed antibiotics (adjusted OR 1.69; 95% CI 0.78 to 3.66). Among these 2 studies, only Dedier et al[21] clearly defined the

Table 2. Assessment of study quality in studies reporting mortality data.

Study, by First Author	Were Patients in Both Groups Equally Likely to Receive Early Antibiotics for Pneumonia?	Was a Valid Severity Instrument Used to Adjust Outcomes (eg, PSI/PORT Score*)?	Was Follow-up Complete?	Were Chart Review Standards Complied With?†
Group A, retrospective studies without severity controls				
Ziss, 2003[20]	No. (Retrospective, CAP patients, *ICD-9* codes. Chart review)	No severity adjustment reported	N/A	B (except exclusion criteria), C
Mortensen, 2004[17]	No. (Retrospective, CAP patients, *ICD-9* codes. Chart review, by random selection)	PSI mentioned, but mortality calculation did not adjust for PSI	N/A	B, C
Wilson, 2005[19]	No. (Retrospective, CAP ICU patients. Chart review, consecutive patients)	PSI mentioned, but mortality calculation did not adjust for PSI	N/A	B, C
Group B, retrospective studies with severity controls				
Meehan, 1997[23]	No. (Retrospective, Medicare claims, *ICD-9* codes. Chart review, by random selection)	Adjusted for PSI class	N/A	A, B, C, D, H (κ=.56)
Dedier, 2001[21]	No. (Retrospective, CAP discharge diagnoses. Chart review)	Adjusted for PSI class	N/A	A, B, C, D
Houck, 2004[22]	No. (Retrospective, Medicare claims, *ICD-9* codes. Chart review, by random selection)	Adjusted for PSI class	N/A	B, C, D, F, H (κ=.80)
Group C, prospective studies without severity controls				
Marrie, 2005[25]	Yes. (Prospectively, at time of floor admission)	PSI mentioned, but mortality calculation did not adjust for PSI	Yes, until discharge (or inpatient death)	N/A
Bodi, 2005[24]	Yes. (Prospectively, at time of ICU admission)	APACHE II score mentioned, but mortality calculation did not adjust for APACHE II	Yes, until ICU discharge (or ICU death)	N/A
Waterer, 2006[26]	Yes. (Prospectively, at time of admission)	Multivariate modeling included altered mental state and other individual predictors. PSI mentioned, but mortality calculation did not adjust for PSI	Yes, until discharge (or inpatient death)	N/A
Group D, prospective studies with severity controls				
Silber, 2003[27]	Yes. (Prospectively, at time of admission)	Adjusted for PSI class	Yes, until discharge (or inpatient death)	N/A

N/A, Not applicable; *APACHE*, Acute Physiology and Chronic Health Evaluation.

*PSI/PORT refers to the validated clinical prediction rule for community-acquired pneumonia.[8]

†Chart review methodology criteria[29]: Training (chart abstractors), case selection (and exclusion), definition of variables, abstraction forms, meetings (abstractors and study coordinators), monitoring (performance of abstractors), blinding (chart reviewers to relation or hypothesis), testing of interrater agreement (κ or other statistic reported).

Table 3. Summary of principal outcome, 4-hour data.*

Study, by First Author	Outcome Definition	Results (OR and 95% CI)
Group A, retrospective studies without severity controls†		
Ziss, 2003[20]	Inpatient mortality	0.82 (0.20–3.40)
Wilson, 2005[19] (ICU only)	ICU mortality	0.24 (0.08–0.71)
Group B, retrospective studies with severity controls†		
Houck, 2004[22] (age >65 y)	Inpatient mortality	0.85 (0.74–0.98)
	30-day mortality	0.85 (0.76–0.95)
Group C, prospective studies without severity controls†		
Marrie, 2005[25]	Inpatient mortality	1.02 (0.77–1.36)
Bodi, 2005[24] (ICU only)	ICU mortality	0.82 (0.54–1.24)
Waterer, 2006[26]§	Inpatient mortality	
	All ages	0.36 (0.15–0.83)§
	Age >65 y	0.34 (0.11–1.09)§
Group D, prospective studies with severity controls‡		
Silber 2003[27]	Inpatient mortality	1.99 (1.22–13.45)‖

OR, odds ratio; *CI*, confidence interval; *y*, years.
*ORs compare short-term mortality in patients receiving antibiotics within 4 hours to that in patients receiving antibiotics later than 4 hours.
†OR not adjusted for Pneumonia Severity Index (PSI) class.
‡OR adjusted for PSI class.
§Effect disappeared after multivariate modeling included altered mental status. Adjusted OR for mortality not reported.
‖Calculated by the authors (see text).

time point from which time to antibiotics was measured and reported a prospective definition of the time cutoff to be used. The prospective study by Marrie and Wu[25] (group C) reported an unadjusted OR for inpatient mortality of 0.96 (95% CI 0.70 to 1.30) for antibiotic treatment within 8 hours compared with antibiotic treatment later than 8 hours. Hence, the 8-hour cutoff data from the studies included in our review are broadly consistent with the pattern emerging from our analysis of the 4-hour cutoff data. Studies with stronger designs, as judged by our prospectively defined criteria, fail to confirm apparent trends in survival benefit of early antibiotic therapy suggested by studies employing weaker study designs.

Three group A studies[15,16,18] report data on the lower-impact outcome of length of hospital stay in community-acquired pneumonia. Lim et al[16] compared pneumonia patients with length of stay greater than 5 days to those with length of stay less than 5 days, finding no significant difference in the proportion that was treated with antibiotics by 8 hours. Rosenstein et al[18] found a 0.8-day shorter length of stay for community-acquired pneumonia patients treated within 2 hours of presentation. Battleman et al[15] compared community-acquired pneumonia patients treated initially in the ED with those treated initially on the inpatient floor, finding that the OR for prolonged length of stay was 1.75 per 8 hours of delay in treatment. Hence, results for this secondary outcome are conflicting across studies within the weakest methodological quality class.

APPLYING THE EVIDENCE

The 54-year-old diabetic man in our clinical scenario who likely, but not yet certainly, has community-acquired pneumonia illustrates a dilemma that can result when regulatory mandates seek to enforce administrative or process requirements that may be at variance with priorities dictated by objective patient severity. Published reports document that the inappropriate use of antibiotics and inaccurate diagnosis are demonstrable consequences of The Joint Commission mandate. Kanwar et al[30] compared community-acquired pneumonia patients admitted to the hospital in 2003 to those admitted in 2005 and observed that compliance with the 4-hour rule increased from 54% in 2003 to 66% in 2005 at the same time that the accuracy of community-acquired pneumonia as a final diagnosis had decreased from 76% in 2003 to 59% in 2005. Other authors have reported that the rate of initial diagnostic uncertainty among patients admitted to hospitals with community-acquired pneumonia exceeds The Joint Commission's target for compliance with the 4-hour mandate.[6,13] Such a disproportion creates an incentive for premature and possibly inappropriate antibiotic use in this population. Finally, some commentators have suggested that the prioritization of clinically stable patients affected by the 4-hour rule over other less stable patients constitutes a potential threat to patient safety.[31]

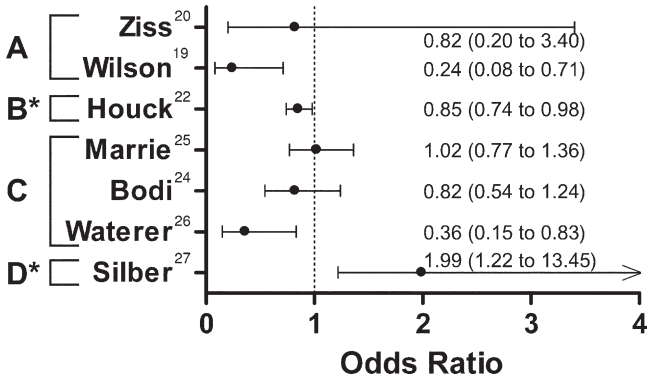

Figure 2. 4-hour time to antibiotics versus mortality. Forest plot of studies reporting inpatient or 30-day mortality in patients with community-acquired pneumonia receiving antibiotics within 4 hours compared to patients receiving antibiotics later than 4 hours. Odds ratios and 95% confidence intervals (CIs) are provided for each study, with the round dots representing the point estimates and the horizontal lines the CIs. Studies identified as A, B, C and D correspond to uncontrolled retrospective studies, controlled retrospective studies, uncontrolled prospective studies and controlled prospective studies, respectively. The adjusted OR for the study by Silber was calculated by the authors.

*severity-adjusted using Pneumonia Severity Index (PSI).

Table 4. Summary of principal outcome, 8-hour data.*

Study, by First Author	Outcome Definition	Results (OR and 95% CI)
Group A, retrospective studies without severity controls†		
Mortensen, 2004[17]	30-Day mortality	0.60 (0.37–1.35)
Group B, retrospective studies with severity controls‡		
Meehan, 1997[23] (age >65 y)	30-Day mortality	0.85 (0.75–0.96)
Dedier, 2001[21]	Inpatient mortality	1.69 (0.78–3.66)
Group C, prospective studies without severity controls†		
Marrie, 2005[25]	Inpatient mortality	0.96 (0.70–1.30)

*ORs compare short-term mortality in patients receiving antibiotics within 8 hours to that in patients receiving antibiotics later than 8 hours.
†OR not adjusted for Pneumonia Severity Index (PSI) class.
‡OR adjusted for PSI class.

Regarding the stable patient in our scenario, should we give him antibiotics even before the diagnosis is confirmed by radiograph? Should we place him in front of other potentially sick patients waiting to be treated? Have we done any harm if he does not have pneumonia? Most important, if our patient has pneumonia, will a further delay in initiating antibiotic therapy likely result in a worse clinical outcome?

Our structured review of published studies on this question demonstrates a wide variability among the results of observational studies comparing inpatient or 30-day mortality to time to antibiotic therapy, using either a 4-hour or an 8-hour cutoff. Indeed, 2 studies[21,27] implied a strong negative effect of early antibiotic administration and were relatively methodologically strong with respect to the standard criteria we used in our review. Observational studies of therapy, even when controlled for known confounders, are notoriously subject to systematic error because of the effect of unequal distribution of variables affecting the likelihood of outcomes of interest. It is perhaps possible, but not intuitively plausible, that early administration of antibiotics to stable patients with pneumonia worsens their chances of survival. However, we believe that it would be no more justifiable to draw such an inference from the observations of the apparently methodologically stronger studies than it would be to infer the opposite from the apparently weaker studies located in our review. We are rather inclined to interpret the results of the studies in question as powerful demonstrations of how difficult it is to control for confounding variables related to clinical outcome in the context of observational studies, even when validated instruments such as that developed by the PORT investigators are used.[8]

The issue of antibiotic timing for patients presenting to EDs with community-acquired pneumonia raises an important distinction between physiologically defined and administratively defined time characteristics. Physiologically based time sensitivity, such as effectiveness of cerebral reperfusion in the first 3 hours after symptom onset in a patient with an acute ischemic stroke,[1] early coronary reperfusion after onset of chest pain in a patient with acute myocardial infarction,[2] or initiation of antibiotic therapy after the initial decrease in blood pressure in a patient with sepsis,[9] directly reflects an underlying disease process. Time from ED arrival of a stable, non–critically ill patient with community-acquired pneumonia to the first dose of antibiotics is an administratively defined characteristic. Such a pneumonia patient has typically been sick for a few days before presentation to the ED, and the timing of presentation is characteristically influenced by factors having little to do with the biological time scale of this disease process.

Before finalizing the conclusions of our own review, we considered the review reported in The Joint Commission specification manual for measurements PN-5 and PN-6.[3] These documents revealed citations of the study by Meehan et al,[23] a preliminary report of the study by Houck et al,[22] and 2 older studies that did not meet the inclusion criteria for our review.[32,33] The Joint Commission reports cited earlier versions of the guidelines for evaluation and management of patients with community-acquired pneumonia published by the Infectious Disease Society of America,[4] guidelines that have subsequently been revised to eliminate a time requirement for initiation of antibiotic therapy in stable patients.[10] The Joint Commission documents did not report the methods used to search and evaluate the literature on this question, nor do they describe how the studies they cite were designed and conducted.[3]

The 2 older studies cited in The Joint Commission report involved before-after designs in which early administration of antibiotics to pneumonia patients was bundled with other process changes, rendering it impossible to derive a comparison of patients receiving early antibiotics to those receiving later antibiotics with respect to short-term mortality.[32,33] Kahn et

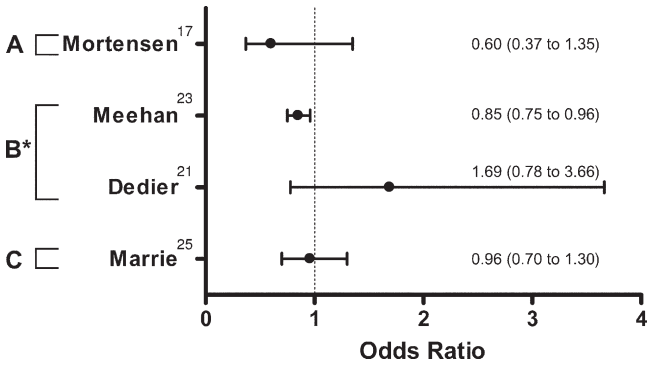

Figure 3. 8-hour time to antibiotics versus mortality. Forest plot of studies reporting inpatient or 30-day mortality in patients with community-acquired pneumonia receiving antibiotics within 8 hours compared to patients receiving antibiotics later than 8 hours. Odds ratios and 95% confidence intervals (CIs) are provided for each study as in Figure 2. Studies are categorized (A, B, C and D) as in Figure 2.

*severity-adjusted using Pneumonia Severity Index (PSI).

al[32] studied outcomes of 5 diseases, including pneumonia, before and after the implementation of the Medicare Diagnosis Related Groups–based prospective payment system, comparing periods 1981 to 1982 and 1985 to 1986. The decrease in 30-day pneumonia mortality (21% to 15%) was correlated with technical therapeutic improvements, ie, a bundle of process changes that combined antibiotic timing with oxygen therapy and intubation. McGarvey and Harper[33] examined the effects of a pneumonia quality improvement initiative at the Forbes Health System in Pennsylvania, noting that observed mortality decreased from 10.2% to 6.8%. Besides correcting delays in initial administration of antibiotics to pneumonia patients, the new clinical pathway required sputum and blood cultures, as well as the addition of legionella and mycoplasma antibiotic coverage to the therapeutic regimen. The latter was done in only 14% of cases before implementation of the clinical pathway. These authors also do not report data allowing the calculation of our outcome measure.

Recently, in September 2007, The Joint Commission specification manual was revised.[34] Citing the latest Infectious Disease Society of America/American Thoracic Society guideline revision,[10] the new manual replaces the original 4-hour time mandate (PN-5b) with a 6-hour mandate (PN-5c). Our review indicates that the evidence supporting a 6-hour or 8-hour mandate is no stronger than that in favor of the original 4-hour mandate.

The patient in our scenario, should his chest radiograph reveal an infiltrate, will be class 3 on the PORT severity scale by virtue of his age, sex, initial blood sugar level, and tachycardia. Given his severity level, combined with his lacking a primary care physician, many emergency physicians would be inclined to admit him for initial intravenous antibiotics and clinical monitoring for improvement. He therefore would fall under the scope of application of The Joint Commission 4-hour mandate. On the other hand, he is stable, is nontoxic, and improves in the course of supportive resuscitation in the ED. Should his chest radiograph result prove negative, many, if not most, practitioners would likely be inclined to discharge him from the ED, perhaps with subsequent monitoring on the part of a primary care provider. Given the conflicting nature of the evidence from clinical research, particularly as it applies to a non–critically ill and nonelderly patient, it would seem unlikely that our patient will benefit significantly from early initiation of a possibly unwarranted course of antibiotic therapy.

In conclusion, the evidence in support of The Joint Commission mandate for initiation of antibiotic therapy to patients with community-acquired pneumonia within 4 hours of arrival to the ED comes from nonrandomized observational studies that are conflicting and that suggest that the association between early antibiotics and mortality diminishes or disappears in studies of higher methodological quality. Although timely administration of antibiotics to patients in the ED with affirmed community-acquired pneumonia is a useful clinical objective, an inflated sense of priority of the 4-hour time frame or premature initiation of antibiotic therapy before confirmation of the diagnosis is not justified by the clinical evidence.

PATIENT COMMUNICATION

Patients are becoming increasingly informed about medical interventions and frequently ask about issues of safety and benefit. The following paragraph is an example of how an emergency physician might convey what is known about the risks and benefits of early antibiotic therapy in patients with community-acquired pneumonia. The details will, of course, be characteristically modified to reflect the actual clinical circumstances.

"Some government agencies have established a goal of beginning antibiotic treatment of patients with pneumonia within 4 hours of hospital arrival. However, the evidence for this rule is not convincing. You have been sick for a few days now and appear relatively well. Waiting a little longer for a chest radiograph, which might not show pneumonia at all, could save you from unnecessary medication and the risk of adverse effects that go along with it."

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Critically Appraised Topic (CAT): Do antibiotics by 4 hours of ED arrival improve pneumonia mortality?

Question	In immunocompetent, moderately but non–critically ill adults being admitted from an ED to the hospital with the primary diagnosis of community-acquired pneumonia, does administration of antibiotics within 4 hours of hospital arrival to the ED decrease inhospital or 30-day mortality compared with administration later than 4 hours after hospital arrival?
Reviewed by	Yu KT, Wyer PC
Expiration date	August 2009
Clinical bottom line	Evidence from nonrandomized trials is inconsistent and suggests the association between early antibiotics and mortality diminishes or disappears as the study quality improves. Stronger studies suggest a minimal or even negative association. Timely identification and treatment of stable patients with community-acquired pneumonia is desirable but should not take precedence over the care of other emergency patients with equal or greater illness severity.
Search strategy	MEDLINE, EMBASE, CINAHL, Emergency Medical Abstracts, Cochrane Central Register of Controlled Trials (CCTR), bibliographies of published guidelines, reviews, included studies, and The Joint Commission specification manual.
Citations	We identified 13 observational studies, of which 10 individual studies allowed calculation of our primary outcome of mortality, and only 4 were prospective studies. 1. Bodi M, Rodriguez A, Sole-Violan J, et al. Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Diseases Society of America guidelines on survival. *Clin Infect Dis.* 2005;41:1709-1716. 2. Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. *Chest.* 2006;130:11-15. 3. 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. 4. 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.
Primary study characteristics	***Study Population*** Immunocompetent adults admitted to the hospital for community-acquired pneumonia ***Interventions*** Antibiotic initiation within 4 or 8 hours of presentation ***Comparisons*** Antibiotic initiation later than 4 or 8 hours ***Outcome Measures*** Inhospital and 30-day mortality
Critical appraisal	Of the 10 trials, 4 were prospective studies, one with severity controls. Time of antibiotic administration was often poorly defined. In the retrospective studies, only 3 of 6 studies complied with more than 2 of 8 published chart review standards.

Results

Study design	Study #	Mortality	OR (95% CI)
4-Hour			
Prospective, no severity controls	1	ICU	0.82 (0.54–1.24)
	2	Inpatient	0.36 (0.15–0.83)*
	3	Inpatient	1.02 (0.77–1.36)
Prospective, with severity controls	4	Inpatient	1.99 (1.22–13.45)†
8-Hour			
Prospective, no severity controls	3	Inpatient	0.96 (0.70–1.30)

*This effect disappeared after limited severity adjustment done by authors.
†Adjusted OR with severity adjustment using Pneumonia Patient Outcomes Research Team score/Pneumonia Severity Index (PSI) class.

APPENDIX E1. Search strategies for large databases (completed August 21, 2006).

MEDLINE (lines 1-36), MEDLINE Prognosis (lines 37-45), EMBASE (lines 46-68), CINAHL (lines 69-76), MEDLINE In-Process & Non-Indexed Citations (lines 77-84), and Cochrane Central Register of Controlled Trials (CCTR, lines 85-91)

1. exp Pneumonia/ use mesz or pneumonia.mp. use mesz
2. exp Community-Acquired Infections/ use mesz or community acquired.mp. use mesz
3. 1 and 2
4. exp Anti-Bacterial Agents/ use mesz or antibiotic$.mp. use mesz
5. 3 and 4
6. exp Pneumonia/dt use mesz
7. 2 and 6
8. 5 or 7
9. limit 8 to (clinical trial or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or validation studies) use mesz
10. exp Epidemiologic Methods/ use mesz
11. Comparative Study/ use mesz
12. 10 or 11
13. 8 and 12
14. 9 or 13
15. 4 h.mp. use mesz
16. 4 hour$.mp. use mesz
17. 8 h.mp. use mesz
18. 8 hour$.mp. use mesz
19. 15 or 16 or 17 or 18
20. 3 and 19
21. exp Time/ use mesz
22. exp Drug Administration Schedule/ use mesz
23. (hour$ or Timing).mp. use mesz
24. 21 or 22 or 23
25. 8 and 24
26. exp Practice Guidelines/ use mesz
27. exp Guideline Adherence/ use mesz or exp Guidelines/ use mesz or pathway$.mp. use mesz
28. 26 or 27
29. 8 and 28
30. exp Emergency Service, Hospital/ use mesz
31. 19 or 24
32. 3 and 31
33. 14 or 20 or 25 or 29 or 32
34. 3 and 30
35. 33 or 34
36. limit 35 to human
37. exp pneumonia/ use mesz or pneumonia.mp. use mesz
38. exp Community-Aquired Infections/ use mesz or community acquired.mp. use mesz
39. 37 and 38
40. limit 39 to ("prognosis (sensitivity)" or "prognosis (specificity)" or "prognosis (optimized)")
41. limit 40 to human
42. 36 or 41
43. remove duplicates from 42
44. 43 not 36
45. remove duplicates from 44
46. [exp PNEUMONIA/ use emez]
47. [(community adj5 pneumonia).mp. use emez]
48. [exp COMMUNITY ACQUIRED PNEUMONIA/ use emez]
49. 46 or 47 or 48
50. [antibiotic$.mp. use emez or exp Antibiotic Agent/ use emez]
51. 49 and 50
52. [exp TIME/ use emez or timing.mp. use emez]
53. [4 h.mp. use emez]
54. [4 hours.mp. use emez]
55. [8 h.mp. use emez]
56. [8 hours.mp. use emez]
57. [hour$.mp. use emez]
58. [drug administration schedule.mp. use emez]
59. [exp practice guideline/ use emez or pathway$.mp. use emez]
60. 52 or 53 or 54 or 55 or 56 or 57 or 58
61. 60 and 51
62. 59 and 51
63. 61 or 62
64. limit 63 to human
65. 36 or 41 or 64
66. remove duplicates from 65
67. 66 not 36 not 45
68. remove duplicates from 67
69. [community acquired.mp. use nursing]
70. [pneumonia.mp. use nursing]
71. 69 and 70
72. limit 71 to human
73. 36 or 41 or 64 or 72
74. remove duplicates from 73
75. 74 not 36 not 45 not 68
76. remove duplicates from 75
77. [community acquired.mp. use prem]
78. [pneumonia.mp. use prem]
79. 77 and 78
80. limit 79 to human
81. 36 or 41 or 64 or 72 or 80
82. remove duplicates from 81
83. 82 not 36 not 45 not 68 not 76
84. remove duplicates from 83
85. [community acquired.mp. use cctr]
86. [pneumonia.mp. use cctr]
87. 85 and 86
88. limit 87 to human
89. 36 or 41 or 64 or 72 or 80 or 88
90. remove duplicates from 89
91. 90 not 36 not 45 not 68 not 76 not 84
92. remove duplicates from 91

APPENDIX E2. Overall search statistics (August 21, 2006).*

Search engine	Librarian-assisted search looking at	Total	Abstracts	Full-Text	In Detail	Included
Ovid MEDLINE	Librarian-assisted search looking at CAP, antibiotics, and timing	1,708	159	81	20	10
Ovid MEDLINE	Simple prognosis search looking at CAP	788	62	22	1	0
Ovid EMBASE	Librarian-assisted search looking at CAP, antibiotics, and timing	1,915	75	39	8	2
Ovid CINAHL	Simple keyword search for CAP	381	62	14	2	1
Ovid MEDLINE In-Process & Non-Indexed	Simple keyword search for CAP	141	14	N/A	0	0
Ovid CCTR	Simple keyword search for CAP	110	3	0	0	0
EM Abstracts	Simple keyword search for pneumonia, antibiotic, and time	50	10	10	0	0
Included Article Bibliographies	Scanning bibliographies of included articles	2	2	2	2	0
Guideline Bibliographies	Scanning bibliographies of established CAP guidelines	0	0	0	0	0
		5,095	387	168	33	13

CAP, community-acquired pneumonia; *N/A*, not applicable; *CCTR*, Central Register of Controlled Trials.

*Searches done sequentially with duplicates removed. Despite this procedure, several duplicates still appeared and were not counted in the final column (number included). Articles without abstracts included in the second column (abstracts). Guidelines examined include Centers for Medicare & Medicaid Services/The Joint Commission, Infectious Disease Society of America 1998/2000/2003, American Thoracic Society 2001, American College of Emergency Physicians 2001, Canadian Infectious Disease Society/Canadian Thoracic Society 2000, British Thoracic Society 2001.