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

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ABSTRACT

This clinical policy from the American College of Emergency Physicians is a revision of the 2009 "Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department With Community-Acquired Pneumonia." A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical questions: (1) In the adult emergency department patient diagnosed with community-acquired pneumonia, what clinical decision aids can inform the determination of patient disposition? (2) In the adult emergency department patient with community-acquired pneumonia, what biomarkers can be used to direct initial antimicrobial therapy? (3) In the adult emergency department patient diagnosed with community-acquired pneumonia, does a single dose of parenteral antibiotics in the emergency department followed by oral treatment versus oral treatment alone improve outcomes? Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

Community-acquired pneumonia remains a major health problem in the United States. As the eighth leading cause of death, it claims the lives of over 100,000 Americans per year.[1] Pneumonia is the most common reason for admission to the hospital, with 1.5 million hospital admissions per year, costing between $11,000 and $51,000 per admission.[2] Because of this profound significance, national quality measures have been developed and refined over the years in an attempt to improve quality of pneumonia care.[3]

Pneumonia is defined as an acute pulmonary parenchymal infection (new lung infiltrate with suspected infectious origin) and although the infectious agent may be nonbacterial, once receiving a diagnosis of pneumonia, the patient is usually treated empirically with antibiotics. Pneumonia can be divided into subcategories (community-acquired, hospital-acquired, and ventilator-associated), with each subcategory carrying different risk factors, morbidity and mortality, and likely pathogens, necessitating varying antimicrobial regimens. In the past, literature has referred to health care–associated pneumonia (HCAP) versus community-acquired pneumonia (CAP). The nomenclature has since been refined, with the HCAP term being retired in favor of 2 subgroups: hospital-acquired pneumonia (HAP), defined as pneumonia not incubating at the time of admission and occurring 48 hours or more after admission, and ventilator-associated pneumonia (VAP), defined as pneumonia occurring greater than 48 hours after intubation.[4] Both of these updated categorizations define pneumonia as being acquired from the hospital admission or from being intubated. This clinical policy focuses solely on CAP.

Clinicians must balance the need to accurately diagnose and treat pneumonia while ensuring that these efforts do not lead to the overuse of antimicrobial therapy. Furthermore, since the majority of admitted patients come through the emergency department (ED), determining patient disposition becomes a major question for emergency physicians. Clinical decision aids and biomarkers may play a role in this effort. Finally, some physicians administer a single dose of intravenous antibiotics before discharge on oral therapy. Whether this practice improves patient outcomes or merely adds to the financial cost, ED length of stay, and patient discomfort remains to be determined.

The 2009 ACEP "Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department With Community-Acquired Pneumonia"[5] addressed questions of whether routine blood cultures were indicated for patients admitted with CAP and whether there was a morbidity and mortality benefit to administering antibiotics in a specific time course. In this updated clinical policy, we address what clinical decision aids can help the emergency physician in the disposition of patients diagnosed with pneumonia, both alone and in conjunction with the use of serum biomarkers. Then we evaluate the use of laboratory testing to direct initial antimicrobial therapy in the ED. Finally, we look at the use of single-dose parenteral antimicrobials before discharging on oral therapy to determine whether there is an outcomes benefit such as decreased length of illness compared with the potential downsides of cost, patient discomfort, and ED length of stay.

METHODOLOGY

This clinical policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of MEDLINE, MEDLINE InProcess, Scopus, EMBASE, Web of Science, and the Cochrane Database of Systematic Reviews were performed. All searches were limited to studies of adult humans published in English. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

This policy is a product of the ACEP Clinical Policy development process, including internal and external review, and is based on the existing literature; when literature was not available, consensus of Clinical Policies Committee members was used and noted as such in the recommendation (ie, Consensus recommendation). Internal and external review comments were received from emergency physicians, clinical pharmacists, specialists in internal medicine, the American Thoracic Society, the Infectious Diseases Society of America, ACEP's Medical-Legal Committee, and ACEP's Quality and Patient Safety Committee. Comments were received during a 60-day open-comment period, with notices of the comment period sent in an e-mail to ACEP members, published in *EM Today*, and posted on the ACEP Web site, and sent to other pertinent physician organizations. The responses were used to further refine and enhance this Clinical Policy; however, responses do not imply endorsement. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this Clinical Policy.

Assessment of Classes of Evidence

Two methodologists independently graded and assigned a preliminary Class of Evidence for all articles used in the formulation of this clinical policy. Class of Evidence is delineated whereby an article with design 1 represents the strongest study design and subsequent design classes (ie, design 2 and design 3) represent respectively weaker study designs for therapeutic, diagnostic, or prognostic studies, or meta-analyses (Appendix A). Articles are then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and conflicts of interest. Using a predetermined process combining the study's design, methodological quality, and applicability to the critical question, articles received a Class of Evidence grade. An adjudication process involving discussion with the original methodologist graders and at least one additional methodologist was then used to address any discordance in original grading, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or ultimately determined to not be applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the background and to inform expert consensus in the absence of robust evidence. Grading was done with respect to the specific critical questions; thus, the Class of Evidence for any one study may vary according to the question for which it is being considered. As such, it was possible for a single article to receive a different Class of Evidence rating when addressing a different critical question. Question-specific Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence grading for each critical question (ie, Evidentiary Table), the subcommittee drafted the recommendations and the supporting text synthesizing the evidence using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of clinical certainty (eg, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies demonstrating consistent effects or estimates).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate scientific certainty (eg, based on evidence from 1 or more Class of Evidence II studies or multiple Class of Evidence III studies demonstrating consistent effects or estimates).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of adequate published literature, based on expert consensus. In instances where Consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

The recommendations and evidence synthesis were then reviewed and revised by the Clinical Policies Committee, which was informed by additional evidence or context gained from reviewers.

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 consistency of results, uncertainty about effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) are

presented to help the reader better understand how the results may be applied to the individual patient. This can assist the clinician in applying the recommendations to most patients but allows adjustment when applying to patients at the extremes of risk (Appendix C).

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. Potential benefits and harms of implementing recommendations are briefly summarized within each critical question.

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 adequate empirical data 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.

This Clinical Policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to answer the critical questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in EDs who evaluate and treat CAP.

Inclusion Criteria. This guideline is intended for adult ED patients with CAP.

Exclusion Criteria. This guideline is not intended for pediatric or pregnant patients.

CRITICAL QUESTIONS

1. In the adult ED patient diagnosed with community-acquired pneumonia, what clinical decision aids can inform the determination of patient disposition?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. The Pneumonia Severity Index (PSI) and CURB-65 decision aids can support clinical judgement by identifying patients at low risk of mortality who may be appropriate for outpatient treatment. Although both decision aids are acceptable, the PSI is supported by a larger body of evidence and is preferred by other society guidelines (ATS/IDSA 2019 guidelines).

Level C recommendations. Among patients not receiving vasopressors or mechanical ventilation, use the 2007 IDSA/ATS Minor Criteria rather than mortality prediction aids such as the PSI or CURB-65 to help establish which patients are most appropriate for care based in an ICU setting (Consensus recommendation).

Do not routinely use biomarkers to augment the performance of clinical decision aids to guide the disposition of ED patients with CAP (Consensus recommendation).

Use CAP clinical decision aids in conjunction with physician clinical judgment in the context of each patient's circumstances when making disposition decisions (Consensus recommendation).

Potential Benefit of Implementing the Recommendations:

- Appropriate use of CAP decision aids may help physicians identify patients who are at low risk for mortality and may be appropriate for outpatient treatment.
- Appropriate use of risk-decision aids may allow physicians to identify patients with CAP who are at high risk for needing mechanical ventilation or vasopressors and who may benefit from ICU admission. Early identification and appropriate disposition of these patients to an ICU is associated with lower mortality compared with patients with delayed transfer to an ICU (ie, after admission to a non-ICU bed).

Potential Harm of Implementing the Recommendations:

- There may be factors pertinent to patient disposition that are not considered by risk-decision aids, such as patients who are immunocompromised or who have poor psychosocial supports. Patients identified as at low risk for mortality may still warrant hospitalization for these reasons. Inappropriate use of risk-decision aids without consideration of external factors could lead to unsafe discharge of patients who should instead be admitted.

Key words/phrases for literature searches: pneumonia, community-acquired, community-acquired pneumonia, CURB, Pneumonia Severity Index, clinical decision support system, clinical decision making, decision support aid, decision support aids, decision support system, decision support tool, decision support tools, clinical decision aid, clinical decision aids, clinical decision tool, clinical decision tools, decision support techniques, decision support systems clinical, emergency, emergency health service, hospital emergency service, emergency ward, emergency medicine, emergency care, emergency treatment, emergency department, emergency room,

emergency service, emergency services, and variations and combinations of the key words/phrases. Searches included January 2007 to search dates of August 29 and 30, 2017.

Study Selection: Six hundred eight articles were identified in the searches. Sixty-six articles were selected from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, zero Class I studies, 2 Class II studies, and 36 Class III studies included for this critical question (Appendix D).

For the last 3 decades, aids that predict CAP-associated mortality have been used to inform decisions regarding the need for hospitalization. Patients with CAP, at low risk of mortality, and who had appropriate social support and outpatient follow-up were typically considered to be appropriate for outpatient management, whereas patients who had higher predicted mortality or insufficient outpatient resources were more often hospitalized. Patients with the highest predicted risk of mortality were often considered for ICU care, although evidence suggests that criteria specifically designed for this purpose (eg, to predict which patients will need ICU-level care such as mechanical ventilation or vasopressors) have greater ability to predict patients who may need these interventions compared with criteria that solely predict mortality. Early identification of patients with CAP who will need ICU care is important because those with delayed ICU transfer from the hospital floor to the ICU, such as for respiratory failure or septic shock, have higher mortality than patients who were admitted directly to the ICU.[6-9]

Two categories of aids help guide these disposition decisions. Traditional clinical decision aids use a combination of patients' clinical signs, laboratory results, and imaging results to inform disposition decisions in conjunction with physician clinical judgment. In recent years, individual laboratory tests "biomarkers" have been identified to inform disposition decisions either independently or in conjunction with clinical decision aids. This review will describe evidence on how ED disposition decisions for patients with CAP may be informed by clinical decision aids, biomarkers, and combinations of them.

Clinical Decision Aids for Mortality in CAP

We identified 7 clinical decision aids that had supporting literature of sufficient methodological rigor for inclusion in this clinical policy evaluation. The first 2, the PSI and the CURB-65, were developed to predict mortality in patients with CAP (Table 1). The evidence for these aids will be presented, after which the remaining 5 clinical decision aids will be described in regard to predicting the need for ICU admission.

Pneumonia Severity Index

The PSI (also known as the Patient Outcomes Research Team, or PORT Score) is a 20-item system originally developed in a Class III study by Fine et al[10] and subsequently validated in a Class II study[11] and several Class III studies.[12-18] The PSI classifies patients into 1 of 5 risk classes with substantially different rates of predicted 30-day mortality. We calculated mortality rate ranges for PSI risk classes among 7 patient cohorts from 5 studies.[10,12-14,16] Patients in risk classes I and II have very low 30-day mortality rates (0% to 0.4% and 0.4% to 1.0%, respectively), and may be appropriate for outpatient treatment. Patients in risk class III have higher 30-day mortality (0.9% to 3.8%) and may be considered for observation or a short hospitalization. Patients in risk classes IV and V (30-day mortality of 6.0% to 11.4% and 16.8% to 38.3%, respectively) are typically admitted for inpatient care. Two Class III multicenter randomized trials and a Class III single-center interventional trial concluded that PSI-based treatment protocols were associated with significantly lower hospitalization rates for low-risk patients and no changes in safety outcomes.[19-21]

CURB-65

Criteria identified by the British Thoracic Society and modified by Neill et al[22] produced the 4-point confusion, urea, respiratory rate, blood pressure (CURB) scale for predicting CAP mortality, and it was subsequently expanded in a Class III study by Lim et al[23] to include an additional criterion for age. The resulting CURB-65 aid was externally validated in Class III studies by Aujesky et al[13] and Capelastegui et al.[14] As with the PSI, the CURB-65 score is directly associated with mortality. Based on 5 patient cohorts from 4 studies, patients with scores of 0 and 1 were found to have very low 30-day mortality rates (0% to 0.7% and 0% to 3%, respectively) and may be considered for outpatient treatment if the physician's clinical judgment deems it appropriate. Patients with a CURB-65 score of 2 have higher 30-day mortality rates (5.9% to 9.2%), and such patients are typically considered for inpatient admission. Patients with scores of 3, 4, or 5 have substantially higher 30-day mortality (13% to 21.4%, 17% to 41.9%, and 14% to 60%, respectively) and warrant hospitalization. There are several variations on the CURB-65, but there are insufficient data to recommend these modified decision aids.[24-27]

Table 1. Mortality prediction aids.

	PSI[10]		CURB-65[23]	
Category	**Specific Criteria**	**Points**	**Specific Criteria**	**Points**
Demographics				
Age		(Age, y)	Age ≥65 y	1
Sex	Female	−10		
Residence	Nursing home resident	10		
Coexisting illnesses				
Neoplastic disease	Present	30		
Liver disease	Present	20		
Congestive heart failure	Present	10		
Cerebrovascular disease	Present	10		
Renal disease	Present	10		
Physical examination				
Mental status	Altered/confused	20	Altered/confused	1
Respiratory rate	≥30 breaths/min	20	≥30 breaths/min	1
Blood pressure	SBP <90 mm Hg	20	SBP <90 mm Hg or DBP ≤60 mm Hg	1
Temperature	<35°C (95°F) or ≥39.9°C (103.8°F)	15		
Pulse	≥125 beats/min	10		
Laboratory and imaging studies				
Arterial pH	<7.35	30		
BUN	≥30 mg/dL (≥11 mmol/L)	20	>7 mmol/L	1
Sodium	<130 mmol/L	20		
Glucose	≥250 mg/dL (14 mmol/L)	10		
Hematocrit	<30%	10		
PaO2	<60 mm Hg	10		
Chest radiograph	Pleural effusion present	10		

PSI Risk Class	30-Day Mortality, %	CURB-65 Score	30-Day Mortality, %
Class I: Age <50 y, no listed illnesses or examination findings	0.1	0	0.6
Class II: ≤70 points	0.6	1	2.7
Class III: 71–90 points	0.9	2	6.8
Class IV: 91–130 points	9.3	3	14.0
Class V: >130 points	27.0	≥4	27.8

Comparison of PSI and CURB-65 for Prediction of Mortality

Several investigations have compared the performance of PSI and CURB-65. In general, both aids should be considered appropriate for prediction of mortality in ED patients with CAP. For instance, Class III studies by Capelastegui et al[14] and Buising et al[28] concluded that the PSI and CURB-65 aids performed similarly for prediction of 30-day and inhospital mortality.

Two studies suggest the PSI may be superior at identifying low-risk patients. Aujesky et al[13] compared the performance of PSI and CURB-65 in a Class III study that defined low-risk patients by using PSI classes I through III and CURB-65 scores of 0 to 1. The negative predictive value for mortality was high for low-risk groups for both the PSI (negative predictive value 99.7%; 95% confidence interval [CI] 99% to 100%) and the CURB-65 (negative predictive value 99.4%; 95% CI 99% to 100%), but the PSI had a statistically greater ability to predict 30-day mortality (area under the curve [AUC] 0.81; 95% CI 0.78 to 0.84) compared with the CURB-65 (AUC 0.76; 95% CI 0.73 to 0.80). Using the above definitions, the PSI identified a higher proportion of patients as low risk (68%) compared with the CURB-65 (61%), and the mortality

rate among patients deemed low risk by PSI (1.4%) was lower than the corresponding mortality rates for low-risk CURB-65 patients (1.7%).[13]

Similar findings were noted by Chalmers et al[15] in a Class III systematic review that compared PSI and CURB-65 aids regarding 30-day mortality. The review identified no statistically significant difference in the aids' performance as measured by summary receiver operating characteristic (sROC) curves (PSI 0.81 versus CURB-65 0.80). However, among low-risk patients (defined as PSI risk classes of I and II or CURB-65 scores of 0 to 1), the PSI had a lower negative LR for mortality (negative LR 0.08; 95% CI 0.06 to 0.12) compared with the CURB-65 (negative LR 0.21; 95% CI 0.15 to 0.30).

As with any clinical decision aid, the PSI and CURB-65 must be used in conjunction with clinical judgment. These aids assist in identifying patients who may be appropriate for outpatient care (ie, are at low risk of short-term mortality) if the treating physician identifies no other significant barriers to treatment. For instance, a patient with a chronic lung disease could have a CURB-65 score of 0 but still require hospital admission for hypoxia. Similarly, patients with a low-risk score may still be appropriate for inpatient care if they have immunosuppression, respiratory muscle weakness, dementia, severe psychiatric illness, housing insecurity, or other contributing medical or psychosocial limitation.[29] Conversely, a patient with a high predicted mortality may still be appropriate for discharge if such a disposition is consistent with patient and family goals of care.

In conclusion, both the PSI and CURB-65 are appropriate aids for predicting CAP mortality. The PSI appears to have slightly greater predictive value for identifying low-risk patients, but this may be offset by the greater number of laboratory studies and longer time needed to complete the PSI compared with the CURB-65.

Clinical Decision Aids for ICU Admission in CAP

Based on the available peer-reviewed research articles that met our methodological quality standards, this review identified 5 clinical decision aids (Table 2) designed to predict whether ED patients with CAP would need ICU care (often referred to as severe CAP). In most cases, readers using a decision aid to help determine the need for ICU care in patients with CAP should use the 2007 criteria from the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) as described below.

American Thoracic Society (2001)

The 2001 ATS guidelines for management of CAP (2001 ATS) stated that patients should be considered for ICU admission if they met at least 1 of 2 major criteria or at least 2 of 3 minor criteria.[30] Since there is little disagreement that patients with either of the 2 major criteria (need for mechanical ventilation or septic shock requiring vasopressors) need ICU care, some critics suggested those criteria added little value when disposition was considered among patients for whom the need for ICU care was less clear. As a result, the 3 minor criteria (systolic blood pressure $\leq$90 mm Hg, multilobar disease, and PaO2/FiO2 ratio $<$250) were subsequently independently evaluated and validated as effective predictors of ICU admission among patients for whom the need for intensive care was not as immediately apparent.[31]

Infectious Diseases Society of America/American Thoracic Society (2007)

In 2007, the ATS produced a revised set of guidelines for CAP in collaboration with the IDSA (2007 IDSA/ATS).[32] These guidelines added 6 new minor criteria, with the recommendation that patients be considered for ICU care if they have at least 1 major criterion or 3 minor criteria. These minor criteria have been validated in several prospective investigations.[33-36] The updated ATS/IDSA guidelines published in 2019 affirmed the use of the minor criteria from the 2007 guidelines.[37]

Severe CAP (CURXO-80)

The severe CAP (SCAP) aid, also known as CURXO-80, was developed by España et al[38] in a Class III observational trial of 1,057 patients designed to predict a combined outcome of inhospital mortality, invasive ventilatory support, or use of vasopressors for shock among patients with CAP. It was subsequently externally validated.[39] The aid includes 2 major and 6 minor criteria, and it recommends that patients be considered for ICU care if they have at least 1 major or 2 minor criteria.

SMART-COP

Charles et al[16] developed the 8-item systolic blood pressure, multilobar chest radiography involvement, albumin level, respiratory rate, tachycardia, confusion, oxygenation, and arterial pH (SMART-COP) scale, which predicts the need for invasive ventilatory or vasopressor support. This aid uniquely uses age-adjusted thresholds for 2 items (respiratory rate and oxygenation) rather than including a variable for age, and it uses different weights (1 point versus 2 points) for different criteria. The scale recommends ICU admission for patients with a score of 3 points or greater.

Table 2. Prediction aids for ICU admission.

	ATS 2001[30]		IDSA/ATS 2007[32]		SCAP (CURXO-80)[38]		SMART-COP[16]		REA-ICU[41]	
Criteria		**Score**		**Score**		**Score**		**Score**		**Score**
Mechanical ventilation	Invasive mechanical ventilation	Major	Invasive mechanical ventilation	Major						
Shock	Septic shock	Major	Septic shock with need for vasopressors	Major						
Blood pressure (BP)	Systolic BP ≤90 mm Hg	Minor	Hypotension requiring aggressive fluid resuscitation	Minor	Systolic BP <90 mm Hg	Major	Systolic BP <90 mm Hg	2		
Radiographic findings	Multilobar disease	Minor	Multilobar infiltrates	Minor	Multilobar or bilateral infiltrates	Minor	Multilobar involvement	1	Multilobar infiltrates or pleural effusion	2
Oxygenation	PaO2/FiO2 <250 mm Hg	Minor	PaO2/FiO2 ≤250 mm Hg	Minor	PaO2/FiO2 <250 mm Hg	Minor	Age ≤50 y: PaO2 <70 mm Hg, SpO2 ≤93%, or PaO2/FiO2 <333 mm Hg Age >50 y: PaO2 <60 mm Hg, SpO2 ≤90%, or PaO2/FiO2 <250 mm Hg	2	PaO2 <60 mm Hg or SpO2 <90%	2
Respiratory rate (breaths/min)			≥30	Minor	>30	Minor	Age ≤50 y: ≥25 Age >50 y: ≥30	1	≥30	1
Mental status			New confusion or disorientation	Minor	Altered mental status	Minor	New-onset confusion	1		
BUN (mg/dL)			≥20	Minor	>30	Minor			>11	1
WBC count (cells/mm^3)			<4,000	Minor					<3,000 or ≥20,000	1
Platelet count			<100,000 cells/mm^3	Minor						
Temperature			<36°C (96.8°C)	Minor						
Arterial pH					<7.30	Major	<7.35	2	<7.35	2
Age (y)					≥80	Minor			<80	1
Albumin (g/dL)							<3.5	1		
Pulse rate (beats/min)							≥125	1	≥125	1
Sex									Male	1
Comorbidities*									1 or more	1
Sodium (mEq/L)									<130	3
Suggested criteria for ICU admission	≥1 major or ≥2 minor criteria		≥1 major or ≥3 minor criteria		≥1 major or ≥2 minor criteria		≥3 points		≥7 points	

*Including cancer, liver disease, kidney disease, stroke, CHF, coronary disease, COPD, or diabetes.

Risk of Early Admission to the ICU

The Risk of Early Admission to the ICU (REA-ICU) aid was developed by Renaud et al[40] to predict ICU admission within 3 days of hospital admission from the ED. Of note, this aid specifically excludes patients with major criteria for ICU admission (eg, need for mechanical ventilation or vasopressors) at ED evaluation. The REA-ICU uses a total of 11 criteria, 8 of which are also used in other CAP risk aids. Each criterion is assigned 1 to 3 points, and patients with 7 or more points are recommended for ICU admission. The aid was externally validated in a Class III study by Labarère et al.[41]

Comparison of Clinical Decision Aids for ICU admission

Several prospective trials and systematic reviews have examined the performance of these ICU-specific aids in relation to the PSI and CURB-65. In general, these studies support the use of aids designed to predict ICU admission, such as the 2007 ATS/IDSA minor criteria to identify patients who may benefit from ICU care, rather than relying on mortality-prediction models such as the PSI or CURB-65. This recommendation is consistent with the recently published 2019 ATS/IDSA guideline.[37] However, no studies have prospectively examined the effectiveness or safety of using these ICU admission decision aids to guide patient management, and thus these recommendations are based on consensus.

Findings from a Class II systematic review and meta-analysis by Marti et al[42] support specific ICU decision aids. For the outcome of ICU admission, higher positive LRs were observed for the full set of 2001 ATS criteria (positive LR 7.3; 95% CI 4.4 to 12.2) and 2007 IDSA/ATS minor criteria (positive LR 5.9; 95% CI 3.8 to 9.3) compared with PSI risk classes IV and V (positive LR 1.5; 95% CI 1.4 to 1.6) or a CURB-65 score of 3 or greater (positive LR 2.1; 95% CI 1.6 to 2.7). The diagnostic odds ratios (ORs), which reflect the ability of these aids to correctly predict which patients were admitted to the ICU and those who were not, were substantially higher for the full 2001 ATS criteria (diagnostic OR 24.6; 95% CI 13.1 to 46.4) and 2007 IDSA/ATS minor criteria (diagnostic OR 13.1; 95% CI 7.7 to 22.3) than for PSI risk classes IV and V of 4 or greater (diagnostic OR 2.9; 95% CI 2.4 to 3) or CURB-65 score of 3 or greater (diagnostic OR 3.6; 95% CI 2.2 to 5.8). Similar conclusions were reached in a 2011 systematic review and meta-analysis by Chalmers et al.[31] The REA-ICU validation study by Labarère et al[41] was not included in either of those reviews but also found similar results, with higher positive LRs for prediction of ICU admission observed for the 2007 IDSA/ATS minor criteria (positive LR 4.1; 95% CI 2.6 to 6.5) and REA-ICU risk classes III and IV (positive LR 3.2; 95% CI 2.3 to 4.5) compared with PSI risk classes IV and V (positive LR 1.5; 95% CI 1.3 to 1.8) or CURB-65 score of 3 or greater (positive LR 1.9; 95% CI 1.2 to 3.0). Together, these results suggest that the 2001 ATS or 2007 IDSA/ATS guidelines may identify patients with CAP to admit to the ICU. Since we are aware of no research that directly compares the minor criteria from the 2001 guidelines with those from the 2007 guidelines, we favor using the 2007 minor criteria because they incorporate a broader set of clinical criteria and are affirmed by the updated 2019 ATS/IDSA guideline.[37]

In other circumstances, emergency physicians may want to identify patients who are the least likely to need ICU care. In the same 2012 study, Marti et al[42] also found that the positive LRs for the SCAP (positive LR 1.8; 95% CI 1.2 to 2.6) and SMART-COP (positive LR 2.6; 95% CI 1.3 to 5.3) aids were no greater than for the PSI and CURB aids, but they both had negative LRs far lower (SCAP negative LR 0.13 [95% CI 0.06 to 0.26]; SMART-COP negative LR 0.15 [95% CI 0.03 to 0.91]) than that of the CURB-65 (negative LR 0.64; 95% CI 0.51 to 0.79), the PSI (negative LR 0.53; 95% CI 0.46 to 0.60), or the 2007 IDSA/ATS minor criteria (negative LR 0.48; 95% CI 0.38 to 0.60). Thus, an emergency physician with several ill CAP patients could use the SCAP or SMART-COP aids to identify patients least likely to need ICU care. However, this area would benefit from additional research. Furthermore, the smaller subsequent study by Labarère et al[41] suggested the negative LRs were somewhat higher for the SCAP (negative LR 0.5; 95% CI 0.4 to 0.8) and SMART-COP aids (negative LR 0.5; 95% CI 0.4 to 0.7) and were not significantly different from the PSI risk classes IV and V (negative LR 0.5; 95% CI 0.3 to 0.8). This study suggested that patients without an REA-ICU score of 4 points or more (a different threshold than noted earlier) had a low negative LR of 0.2 (95% CI 0.1 to 0.5) but this finding has not been reproduced elsewhere.

In conclusion, we suggest the 2007 IDSA/ATS minor criteria may add to physician clinical judgment for identifying patients with CAP who are most likely to need ICU care.[32] We are aware of no prospective data on the effectiveness or safety of using these aids to inform patient disposition, and this limitation reinforces the importance of using these aids in conjunction with physician clinical judgment.

Limitations of CAP Clinical Decision Aids

Physicians must be aware of the broader medical and psychosocial factors that may influence the decision to pursue inpatient versus outpatient care, and patients with

low predicted mortality may nonetheless warrant hospital admission.[43-45] For instance, these aids have not been validated and should not be used for patients who are immunocompromised or who were recently discharged from the hospital. Patients may not be appropriate for outpatient treatment if they are unable to receive oral antibiotics (eg, due to severe nausea or vomiting) or if they have significant psychosocial comorbidities such as psychiatric disease or homelessness. Physician clinical judgment may identify patients who warrant admission due to factors beyond those addressed by these aids.

Biomarkers

This review identified 12 laboratory markers that have been investigated for their prognostic value in CAP. Our review focuses primarily on the 2 biomarkers with the largest body of supportive research, midregional pro-adrenomedullin (MR-proADM) and procalcitonin (PCT). Research suggests the prognostic value for these 2 biomarkers may be as good as, but no better than, that of the PSI and CURB-65, and there are only limited data on using biomarkers and clinical decision aids together to inform disposition of patients with CAP. Since biomarkers do not presently offer an advantage over the clinical decision aids for informing CAP disposition, there is little justification for their use in clinical practice and additional costs from these tests may be substantial. In addition, we are aware of no prospective studies evaluating the effectiveness or safety of using biomarkers (either alone or together with clinical decision aids) to guide the initial site of treatment for CAP. As a result, we recommend neither of these biomarkers be used to guide disposition for patients with CAP unless future research determines they can significantly improve patient outcomes. For the remaining 10 biomarkers, there was either insufficient literature on test performance or evidence suggesting poor prognostic value for guiding disposition in CAP.[46-58]

MR-proADM levels correlate well with PSI score, as demonstrated in Class III investigations by Christ-Crain et al,[51] Courtais et al,[52] and Huang et al.[59] Two Class III studies by Christ-Crain et al[51] and España et al[60] found that MR-proADM levels at hospital admission were higher in patients with CAP who subsequently died or developed complications compared with survivors. However, Class III studies by Courtais et al,[52] and Huang et al,[59] and España et al,[60] showed that the value of MR-proADM to predict mortality or ICU admission was not statistically different from that of the PSI and CURB-65.

Procalcitonin appears to have some prognostic value for mortality in CAP, albeit not as much as MR-proADM. The previously referenced Class III studies by Christ-Crain et al,[51] Courtais et al,[52] and Huang et al[61] found initial PCT levels were higher among CAP patients who died during follow-up than among survivors and that PCT correlates with PSI risk classes but to a lesser degree than MR-proADM. Similarly, 2 Class III studies suggested PCT had less prognostic value for 30-day mortality compared with MR-proADM.[59,60] A large Class III study found a linear association between PCT concentration and need for invasive respiratory or ventilator support in patients with CAP, with a 1% to 2% increased risk of this combined outcome for each 1 ng/mL rise in PCT (up to 10 ng/mL).[62] However, the overall prognostic value of PCT appears to be statistically no different than that of PSI or CURB-65 for prediction of 30-day mortality.[61]

Performance of Clinical Decision Aids and Biomarkers Together

In general, studies that examine addition of biomarkers to mortality-decision aids (eg, PSI or CURB-65) have shown either small or negligible improvement to overall aid performance. A single-center Class III study of 302 patients at a single institution suggested that a combined aid of MR-proADM and PSI was slightly better than PSI alone (AUC 0.77 versus 0.73).[51] However, a large Class III prospective cohort study of 1,653 patients at 28 EDs concluded that a combined MR-proADM/PSI aid was no better than the PSI alone (AUC 0.84 versus 0.83).[59] Similarly, the addition of PCT to the PSI appears to have no additional benefit above the PSI alone in predicting mortality across all patient groups (AUC 0.85 versus 0.83).[61]

A small body of literature suggests that biomarkers may have more value when used selectively in high-risk patients. For instance, a Class III prospective cohort study of 109 CAP patients identified that MR-proADM levels varied little among low-risk patients (PSI risk classes I through III) but varied substantially among high-risk patients (PSI risk classes IV and V).[52] Among these high-risk patients, logistic regression demonstrated MR-proADM levels were significantly associated with 30-day mortality, whereas the absolute PSI scores (IV versus V) were not. A large multicenter Class III prospective cohort study found similar results; among patients in high-risk PSI classes (IV and V), individuals with MR-proADM levels in the lower 3 quartiles had significantly lower mortality rates compared with those with MR-proADM levels in the top quartile (9% versus 23%).[59] Other research has found similar associations for PCT. A large Class III prospective cohort study concluded that patients in high-risk PSI classes with PCT levels in the highest quartile had a substantially higher

mortality rate than those with PCT levels in lower quartiles (19.0% versus 1.6%), resulting in a negative LR of 0.09 (95% CI 0.02 to 0.36) for patients with lower PCT levels.[61] Similar but slightly weaker trends were seen among patients with high-risk CURB-65 scores and low PCT levels (negative LR 0.18; 2.2% versus 13.8%).

For prediction of ICU admission, there is very limited literature on the value of combining biomarkers with clinical decision aids. In a Class III study, España et al[60] examined the value of 3 biomarkers (MR-proADM, PCT, and C-reactive protein) in conjunction with 3 risk-stratification aids (PSI, CURB-65, and SCAP) to predict ICU admission and other SCAP-associated complications. This investigation concluded that MR-proADM improved the AUC for all 3 aids: SCAP improved from 0.83 to 0.88, PSI improved from 0.83 to 0.87, and CURB-65 improved from 0.79 to 0.85. PCT added prognostic value to all 3 aids but to a lesser degree.[60]

A single-center Class III study by Chen and Li[46] added a lactate measurement to the CURB-65 score and examined the prognostic value of this revised aid. Results suggested this approach could offer additional prognostic value to the CURB-65 for this purpose, but the results were not compared with the ICU-decision aids (eg, 2001 ATS or 2007 IDSA/ATS aids) and they have not been replicated at other centers.

Summary

The PSI and CURB-65 are both well-validated aids that can predict short-term mortality in patients with CAP and can be used to identity low-risk patients for whom outpatient management may be considered. Both aids are appropriate for this purpose in the emergency care setting; the PSI appears to be slightly better at identifying low-risk patients, but it requires data from a greater number of tests, including some not routinely conducted in the ED (ie, arterial blood gases). For decisions regarding ICU admission, aids designed for this purpose should be considered superior to the PSI and CURB-65. In particular, the 2007 IDSA/ATS minor criteria offer high positive LRs and high diagnostic ORs for prediction of ICU admission, although this recommendation is based on consensus because to our knowledge no studies have examined the effectiveness or safety of patient management based on these criteria. MR-proADM and PCT biomarkers appear to have prognostic values that approach but do not exceed that of the clinical decision aids, and there is insufficient literature on using biomarkers in conjunction with established CAP clinical decision aids. Additional research may help clarify the role of these newer clinical decision aids and biomarkers in the disposition of ED patients with CAP.

Future Research

The body of research on these decision aids would be strengthened by additional research to compare their performance with physician clinical gestalt alone. Additional validation studies on the SCAP, SMART-COP, and REA-ICU aids may help clarify the value of these aids and potentially expedite their adoption into clinical practice. Furthermore, additional validation studies are needed for the prognostic value of biomarkers in conjunction with clinical decision aids. There is a particular need to identify the subset(s) of patients for whom biomarker results can meaningfully influence decisions regarding patient disposition from the ED.

2. **In the adult ED patient with community-acquired pneumonia, what biomarkers can be used to direct initial antimicrobial therapy?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Do not rely upon any current laboratory test(s), such as procalcitonin and/or C-reactive protein, to distinguish a viral pathogen from a bacterial pathogen when deciding on administration of antimicrobials in ED patients who have CAP.

Potential Benefit of Implementing the Recommendations:

- Laboratory testing can be costly, painful to the patient, dangerous to clinicians (needlestick exposure), and can also result in delays in treatment and disposition of patients in the ED. By avoiding testing that does not conclusively decrease antibiotic use, patient evaluation and treatment may proceed in a more time-efficient manner.

Potential Harm of Implementing the Recommendations:

- None.

Key words/phrases for literature searches: pneumonia, community-acquired, community-acquired pneumonia, community-acquired infections, C reactive protein, C-reactive protein, procalcitonin, pro-calcitonin, antigens, bacteria, urine, emergency, emergency health service, hospital emergency service, emergency ward, emergency medicine, emergency care, emergency treatment, emergency department, emergency room, emergency service, emergency services, emergency medical services, and variations and combinations of the key words/phrases. Searches included January 1, 2007, to search dates of August 31, 2017, and September 1, 2017.

Study Selection: Four hundred sixty-three articles were identified in searches. Twenty-seven articles were selected

from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, zero Class I studies, 3 Class II studies, and 2 Class III studies included for this critical question (Appendix D).

Community-acquired pneumonia has traditionally been treated empirically with antibiotics even with the suspicion that viral pathogens are responsible for a percentage of the cases. Recent studies have suggested that viral pathogens may be the predominant cause of CAP.[63] In one of the largest epidemiologic studies to date, Jain et al[63] evaluated 2,488 patients with CAP, of whom 93% had radiographic evidence of pneumonia (eg, infiltrate, effusion). Despite using a battery of available laboratory testing (eg, polymerase chain reaction (PCR), bacterial and viral culture, urinary antigens), only 38% of cases had a definitive cause identified. The predominant identified cause was viral, at 23% (human rhinovirus 9%, influenza 6%, and other 8%), whereas bacterial pathogens were identified in 11% of patients (predominant strain *Streptococcus pneumoniae,* at 5%). Interest in antibiotic stewardship has led to a surge in research to distinguish viral from bacterial pathogens in order to prescribe antibiotic therapy only to those patients who will receive benefit. This second critical question related to CAP was specifically selected to identify ED patients who are more likely to have a bacterial pathogen as the cause of their CAP.

In total, 27 articles were graded by our methodologists and the majority of these articles (22) were found to have fatal flaws and assigned a final grade of "X." Two articles[64,65] were given a final grade of Class II, but because each article reflected the same meta-analysis published in 2 separate journals, only 1 was included in our discussion.[64] The 4 articles that are summarized later are heterogeneous in nature in both their study groups and in their primary endpoints, which made it challenging to compile a summative statement regarding this critical question. The articles involved ED patients, inpatients, and non-ICU patients. Furthermore, the primary endpoints were disparate: mortality in the Cochrane review and total length of antibiotic duration in the 2018 *New England Journal of Medicine* study.[66] Another limitation is that numerous studies investigated both individual and combinations of laboratory markers.

The majority of the research has focused on PCT and C-reactive protein (CRP). Procalcitonin is a calcitonin-related biomarker released in response to bacterial infection and tissue injury and is downregulated in viral infections.[65] Research on PCT as an aid to identify bacterial causes of lower respiratory tract infections (LRTIs) has been ongoing for more than a decade.[67-70] Procalcitonin has also been evaluated to assist in the decision to initiate antibiotic therapy,[71] to identify potential bacterial cause in the patient with undifferentiated fever in the ED,[72-78] and to determine who will benefit from antibiotic use in acute exacerbations of chronic obstructive pulmonary disease (COPD).[79-81] C-reactive protein is a non-specific inflammatory biomarker that increases as a result of numerous infectious and noninfectious pathologies that result in systemic inflammation.[82] Research involving CRP has investigated its use in differentiating bacterial from viral pneumonia,[70,78,83-87] distinguishing pneumonia from heart failure,[88] and limiting antibiotic use in patients with bronchitis.[89]

In 2017, a Class II Cochrane review was published by Schuetz et al[64] evaluating the use of PCT on initiating or discontinuing antibiotics in patients with acute respiratory infections in regard to mortality and treatment failure. The authors included 26 trials and a total of 6,708 patients. The heterogeneous patient population with acute respiratory infection included patients with CAP, hospital-acquired pneumonia, ventilator-associated pneumonia, acute bronchitis, exacerbation of COPD, and upper respiratory infections. The majority of trials (24 of 26) enrolled patients in the ED, ICU, or both settings. The 30-day mortality was significantly lower for patients who had PCT-guided care in regard to antibiotic use versus the control group (8.6% versus 10.0%; adjusted OR 0.83; 95% CI 0.70 to 0.99). There was no difference in treatment failures (adjusted OR 0.90; 95% CI 0.80 to 1.01), but the PCT-guided care group had a 2.4-day reduction in antibiotic exposure (95% CI –2.71 to –2.15) and a reduction in antibiotic-related side effects (16.3% versus 22.1%; adjusted OR 0.68; 95% CI 0.57 to 0.82).

In 2018, a large Class II randomized controlled trial by Huang et al[66] (ProACT study) examined the effect of a PCT-based algorithm on the antibiotic prescription in patients with suspected acute LRTI in the ED setting. The study involved 14 US hospitals and 1,656 adult patients ($\geq$18 years) who were randomized to usual care (clinician discretion on antibiotic use for LRTI) or a PCT-level-based group. Clinicians in the PCT group were given PCT levels and the recently approved Food and Drug Administration guideline regarding PCT levels in LRTI indicating whether antibiotics are strongly discouraged, discouraged, recommended, or strongly recommended. Clinicians were not mandated to adhere to the guideline; however, 72.9% of emergency physicians did adhere to it. Final diagnoses for patients (some patients received more than 1 final diagnosis) included CAP (19.9%), acute exacerbation of COPD (31.9%), acute exacerbation of asthma (39.3%),

and acute bronchitis (24.2%). The primary outcome was total antibiotic days in the 30-day period following enrollment. There were 826 patients in the PCT intervention group and 830 patients in the control group. At 30 days, the percentage of patients who had received antibiotics in the PCT intervention group was 471 (57.0%) versus 513 (61.8%) in the control group (99.86% CI –12.7% to 3.0%). The PCT intervention group received antibiotics for a mean of 4.2 days and the control group received them for a mean of 4.3 days (95% CI –0.6 to 0.5). The secondary outcome of adverse outcomes was evaluated for noninferiority with a prespecified noninferiority margin of 4.5 percentage points. The secondary outcome of adverse outcomes was met in 11.7% of patients in the PCT intervention group and 13.1% (95% CI –4.6% to 1.7%) of patients in the control group. When the patient cohorts were evaluated by subgroup (CAP, acute exacerbation of COPD, acute exacerbation of asthma, and acute bronchitis), there was no statistical difference between the PCT intervention group and the control group. The authors concluded that a PCT-based algorithm did not result in lower use of antibiotics in ED patients with suspected LRTI.

In a 2007 Class III study by Müller et al,[90] data from 545 patients were evaluated as part of a post hoc analysis of 2 prior studies. Of the 545 patients, 373 had a final diagnosis of CAP, whereas the other 132 had a final diagnoses of bronchitis, acute exacerbation of COPD, or asthma exacerbation. Both PCT and high-sensitivity CRP were evaluated in adult patients with suspected LRTI in their capacity to accurately identify CAP, predict bacteremia, and assess severity of CAP. The authors evaluated PCT and high-sensitivity CRP in patients with and without radiographic findings consistent with CAP. Although both PCT and high-sensitivity CRP increased the likelihood of accurately identifying CAP, PCT performed better than high-sensitivity CRP and was also beneficial in predicting bacteremia and severity of illness (ie, higher PCT levels correlate to higher morbidity and mortality).

The final graded article (Class III) by Rainer et al[91] investigated both CRP and neopterin levels in regard to their ability to identify a bacterial source of acute respiratory tract infections (ARTIs). Neopterin is an inflammatory marker produced by macrophages and monocytes in response to inflammation, with increased levels seen in viral as opposed to bacterial pathogens. The cohort involved 561 adult patients with ARTIs who presented to the ED. They found that patients ultimately diagnosed with a bacterial source of ARTIs had a CRP/neopterin ratio 10 times higher than that of patients diagnosed with a viral source of ARTIs. Using a receiver operator curve, they determined the optimal cutoff ratio for CRP/neopterin ratio was greater than 3 to produce a 79.5% sensitivity and greater than or equal to 81.5% specificity for ruling in bacterial ARTIs.

Summary

There has been considerable research investigating adjunctive laboratory markers to assist in identifying bacterial causes of CAP in the ED. However, very few of these studies are of adequate quality to be included in this analysis. Even the graded articles included in this review have major flaws highlighted by the heterogeneous patient populations. The researchers included patients who had COPD, bronchitis, upper respiratory infections, and asthma exacerbations in the same cohort, making any conclusion about laboratory markers in CAP unreliable. Procalcitonin has received considerable attention in the past decade for its potential role in identifying a bacterial source of LRTI. However, in relation to specifically its utility in the ED, the literature is of insufficient quality to adequately conclude how an emergency physician may use PCT when evaluating patients with suspected CAP and determining which patients would benefit from antibiotics.

Future Research

Recent research has explored alternative laboratory markers such as ischemia-modified albumin,[92] delta neutrophil index,[93] and inflammatory marker triggering receptor on myeloid cells (TREM-1).[94] Perhaps most intriguing of all novel assays is the advance of multiplex polymerase chain reaction (PCR) respiratory panels using nasal swab specimens to detect viral and bacterial pathogens.[95,96] The film array respiratory panel is still being investigated for cost, feasibility, and efficacy in the ED setting.

3. In the adult ED patient diagnosed with community-acquired pneumonia, does a single dose of parenteral antibiotics in the ED followed by oral treatment versus oral treatment alone improve outcomes?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Given the lack of evidence, the decision to administer a single dose of parenteral antibiotics prior to oral therapy should be guided by patient risk profile and preferences (Consensus recommendation).

Potential Benefit of Implementing the Recommendations:

- Improved patient satisfaction and compliance as a result of more efficient patient care and shared decision making.

Potential Harm of Implementing the Recommendations:

- Increased cost and health care resource utilization.
- Increased ED length of stay, depending on antibiotic selection and duration of administration.
- Complications from potentially otherwise unnecessary intravenous catheter placement (superficial venous thrombosis, infiltration, pain, localized infection).

Key words/phrases for literature searches: pneumonia, community-acquired, community-acquired pneumonia, antibiotic, antibiotic agent, antibacterial agents, antibacterial drugs, oral, oral drug administration, infusion, intraarterial infusion, intraarterial drug injection, intravenous infusion, parenteral infusion, injection, intramuscular injection, intramuscular drug injection, intravenous injection, intravenous, IV, intravenous drug administration, parenteral, parenteral infusion, parenteral drug administration, and variations and combinations of the key words/phrases. Searches included January 1, 2007, to search dates of August 31, 2017, September 1, 2017, and September 7, 2017.

Study Selection: One thousand three hundred ninety-seven articles were identified in the searches. Three articles were selected for further review. After grading for methodological rigor, zero studies were included for this critical question (Appendix D).

Appropriately selected antibiotics are the standard treatment for CAP, with outpatients generally treated orally and those requiring admission generally initially treated parenterally. Multiple studies have demonstrated the safety and efficacy of initial parenteral antibiotics in adult ED patients admitted for CAP with an early transition to oral therapy.[97-102] These studies used various criteria to define when the parenteral to oral therapy switch should occur, but most mandate the patient be clinically stable and afebrile for a minimum of 24 to 72 hours. Patients enrolled in these studies received multiple doses of parenteral antibiotics prior to switching to oral antibiotics. With appropriate application of clinical decision aids, an increasing proportion of patients may be treated as outpatients or with periods of observation (<24 hours). In those patients requiring observation or for whom a brief admission or discharge is deemed to be a reasonable option (borderline cases), it would be reasonable to consider an initial parenteral dose of antibiotics prior to conversion to oral therapy. Our systematic review of the literature, however, found lack of evidence that assessed whether a single dose of parenteral antibiotics in the ED followed by oral treatment was safe or associated with improved outcomes when compared with oral treatment alone among patients either being admitted or discharged home.

Summary

There is lack of evidence to support or refute that the use of a single dose of parenteral antibiotics in adult ED patients with a diagnosis of CAP followed by oral treatment with antibiotics improves outcomes compared with oral treatment alone. Clinicians may consider using this practice guided by patient risk profiles and preferences and should engage in shared decision making.

Future Research

Future studies should assess whether administration of a single dose of parenteral antibiotics and continued observation for stability may ultimately provide safe, efficacious, and cost-effective treatment for adult patients for whom the decision to admit or discharge is unclear (ie, those in a clinical decision unit or observation unit). If future research demonstrates a benefit of a single parenteral dose of antibiotics prior to discharge with oral antibiotics, inpatient admissions may be safely avoided.

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members for this topic.

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.

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Appendix A. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series	Case series	Case series

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing 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.

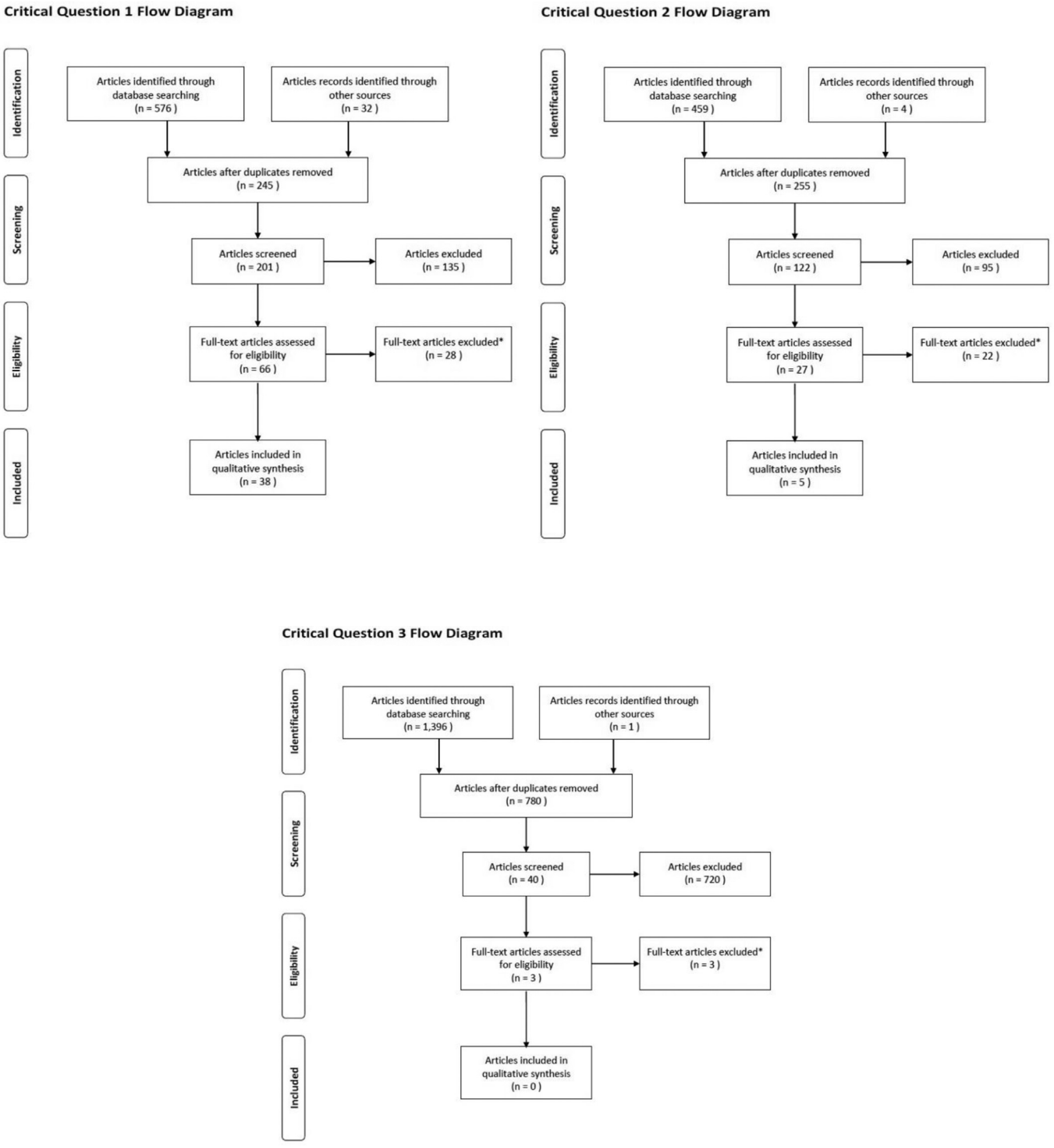
	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

Appendix C. Likelihood ratios and number needed to treat.*

LR (+)	LR (–)	
1.0	1.0	Does not change pretest probability
1–5	0.5–1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostict
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

APPENDIX D. PRISMA[103] FLOW DIAGRAMS..



*Articles identified with fatal flaws or ultimately determined to not be applicable to the critical question. See "Methodology" section for more detail.

Evidentiary Table

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Fine et al[10] (1997)	III for Q1	Hybrid, retrospective and prospective observational; derivation cohort: adult inpatients with CAP; excluded those with HIV, recent admission, or transfers; 78 hospitals in 23 states; validation cohort: adult patients hospitalized with CAP in Pennsylvania and a prospective cohort of adult patients with CAP from 5 institutions, using both outpatients and inpatients	Derivation cohort; chart abstraction; 250 candidate predictive variables; outcome, 30-day mortality	Derivation: 14,199 patients (retrospective); validation: 38,039 patients (retrospective), 2,287 patients (prospective); instrument includes age, comorbidities, physical examination findings, and laboratory findings; derived and validated a clinical prediction instrument with 5 risk classes: I, mortality: 0.1% to 0.4% II, mortality: 0.6% to 0.7% III, mortality: 0.9% to 2.8% IV, mortality: 8.2% to 12.5% V, mortality: 27.0% to 31.1%	Limited methodological detail; derivation among large administrative data sets but validated among a prospective cohort

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Carratalà et al[11] (2005)	II for Q1	Randomized clinical trial conducted at 2 tertiary care hospitals (1 academic and 1 urban) in Barcelona, Spain, between October 2000 and October 2002	Enrolled patients >18 y with diagnosis CAP; excluded if immunosuppressed; patients with CAP were stratified into risk classes by PSI scores; patients in risk classes I, IV, and V were excluded; patients in risk classes II and III were randomized; primary outcome percentage of patients with an overall successful outcome defined as meeting all 7 criteria: (1) cure of PNA, (2) absence of adverse drug reactions, (3) absence of medical complications during treatment, (4) no need for additional visits, (5) no changes in initial treatment with levofloxacin, (6) absence of subsequent hospital admission in the 30 days after randomization, and (7) absence of death from any cause in the 30 days after randomization	A total of 224 patients were enrolled; N=203 analyzed; of these, 110 received outpatient care and 114 were hospitalized; 21 patients were excluded for protocol breaches not following eligibility criteria; overall successful outcome was achieved in 83.6% of outpatients and 80.7% of hospitalized patients (absolute difference 2.9 percentage points; 95% CI –7.1 to 12.9 percentage points)	Small sample size; complex primary endpoint; examined only PSI classes II and III; study not blinded but had concealed allocation

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Armour et al[12] (2003)	III for Q1	Multicenter prospective observational study at primary care practice clinics or emergency departments at 9 medical centers (5 community healthcare systems, 3 university-affiliated hospital systems, and 1 Veterans Affairs Medical Center) in Georgia and Virginia in the US between November 1996 and March 1998	Eligible patients: 18 to 50 y with any risk factors (cancer, congestive heart failure, stroke, chronic kidney disease, liver disease, altered mental status, tachycardia, tachypnea, fever, or hypotension); or patients 50 to 80 y with none of the above factors; initial diagnosis may have been on clinical grounds; all patients received CXR within 2 days of presentation; patients excluded if coming from skilled nursing facility or other facility, if previously hospitalized within 10 days, known history of HIV, was an organ transplant recipient, or was receiving dialysis for end-stage renal disease; calculated PSI for each patient; primary outcome: 30-day mortality; missing data handled by assigning lowest-risk score for categories with missing data; patients in PSI class I and V (calculated after enrollment) excluded from analysis	Enrolled 675 patients; PSI AUC for predicting mortality was 0.75; mortality by PSI class: class II, 1.0% (95% CI 0.3% to 3.0%); class III, 2.4% (95% CI 0.8% to 5.4%); class IV, 11.4% (95% CI 7.1% to 17.1%); total 4.1% (95% CI 2.8% to 5.9%)	Excluded PSI classes I and V cases after enrollment, selection bias may be introduced; logistic regression models used for binary outcomes conceivably for each category instead of running ordinal logit models; outpatient and inpatient status included, but unclear whether the rule also determined or influenced disposition decisions; industry sponsored

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Aujesky et al[13] (2005)	III for Q1	Multicenter prospective cohort study; 32 EDs in Pennsylvania and Connecticut	Eligibility: patients 18 y or older, clinical diagnosis of PNA, and a new radiographic pulmonary infiltrate; excluded if considered to have HAP, immunosuppression or comorbid conditions that distinguished them diagnostically or therapeutically from PNA, or psychosocial problems incompatible with outpatient treatment, enrollment, or follow-up; outcome: all-cause mortality within 30 days; excluded patients whose mortality status could be not be ascertained; any missing variables in the PSI or CURB scores were assumed to be normal: based on commonly accepted definitions of low-risk patients (PSI risk classes I through III; CURB scores <1; and CURB-65 scores <2); estimated sensitivity, specificity, and positive and negative predictive values for cut points defining high risk; assessed discriminatory power with AUC analysis	N=3,181 patients; overall 4.6% mortality within 30 days; at every threshold, PSI had a higher sensitivity and a lower specificity than CURB scores; >95% NPV across all thresholds for all prediction rules; positive predictive values were low; the PSI had a greater discriminatory power to predict 30-day mortality than CURB scores: PSI 0.81, CURB 0.73, CURB-65 0.76	Secondary analysis of clinical pathway studies for PNA; unclear how this biased results; excluded individuals for whom mortality data were missing; N=57, could have biased results; unclear whether sampling was random or all were approached; unclear attrition among those who were approached; missing data assumed to be normal rather than using multiple imputation or sensitivity analysis; decision to drop those for whom mortality data could not be ascertained is problematic, could have checked death records; 30-day mortality was lower (4.6%) than in previous studies of PNA prognosis focused on inpatients; spectrum bias inflated NPVs for all rules compared to prior studies; industry sponsored

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Capelastegui et al[14] (2006)	III for Q1	Single-center prospective cohort study; public 400-bed teaching hospital in Northern Spain	Adults >18 y admitted to the hospital's ED with a diagnosis of CAP; excluded if immunosuppressed or admitted to hospital in last 14 days; PSI, CURB-65, and CRB-65 calculated for all patients	A total of 1,776 patients: 1,100 inpatients (61.9%) and 676 outpatients (38.1%); of these, 1,724 (97.1%) had data sets for all risk scores under evaluation; 30-day mortality rate in the entire cohort was 6.7%; AUC for predicting 30-day mortality: PSI AUC 0.89 (95% CI 0.86 to 0.91); CURB-65 AUC 0.87 (95% CI 0.84 to 0.90); CRB-65 AUC 0.86 (95% CI 0.84 to 0.89); the 474 patients with CURB-65 scores of 2 were distributed in 2 subgroups, with statistically significant ($P<.001$) differences in 30-day mortality: 40.9% in PSI risk classes I through III (2.6% 30-day mortality), and 59.1% in PSI risk classes IV and V (11.1% 30-day mortality); among patients with CURB-65 scores of 3 to 5, 92.6% (274 of 296 patients) belonged to PSI risk classes IV and V, with 30-day mortality rates of 28.5%	Secondary analysis of a clinical protocol implementation study; CURB scores retrospectively applied for risk severity, but disposition decisions may have affected results; chart review was used to ascertain variables and scored normal if data were missing

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Chalmers et al[15] (2010)	III for Q1	Meta-analysis of prospective and retrospective studies published between 1980 and August 2009	Objective to assess differences in performance between the PSI, CURB-65, and CRB-65 risk scores in predicting mortality from CAP; followed MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines; used PubMed and EMBASE; included all languages; excluded conference abstracts; 2 investigators independently assessed article eligibility and quality using modified Hayden criteria, tables included; pooled estimates for outcomes ratios, sensitivity, specificity, positive and negative LRs reported from random-effects models stratified by risk categories; heterogeneity assessed using Cochran Q test and Higgins I^2 test	N=40 studies identified meeting eligibility criteria; 17 studies reported data for CURB-65, 11 studies reported data for CRB-65, and 31 articles reported data for PSI, comprising 33 individual cohorts; the majority of studies used 30-day mortality as their primary outcome measure, although inhospital mortality was used in a few studies; there were no significant differences in the AUC curves between PSI, CURB-65, and CRB-65 in the main analysis or in any of the extensive subanalyses; PSI had a superior negative LR and identified a higher percentage of patients as low risk compared with CURB-65 and CRB-65; the high risk groups of CURB-65 and CRB-65 had a higher positive LR	Inconsistent outcome use; significant heterogeneity in all analyses of discrimination; no sensitivity analysis was undertaken using higher-quality studies

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Charles et al[16] (2008)	III for Q1	Multicenter prospective cohort study in Australia	Included adult ED patients with CAP who were admitted; positive prediction of IRVS; derived SMART-COP rule and validated it in 5 historical cohorts; also evaluated PSI and CURB-65 rules	IRVS required in 91 of 882 episodes (derivation) and patients; in derivation cohort, AUC 0.87 to predict IRVS; for threshold of 3, sensitivity 92% (95% CI 85% to 97%) and specificity 62% (95% CI 59% to 66%); in validation cohorts, predictive ability was generally worse	Predictor and outcome variables were not measured in blinded fashion; cohort only includes patients who were admitted
Akram et al[17] (2011)	III for Q1	Systematic review and meta-analysis	Included original studies with at least 20 outpatients with CAP; excluded non-CAP diagnoses; and calculated severity scores (PSI, CRB-65, CURB-65); included patients managed exclusively as outpatients or those treated in ED and discharged from ED within 24 h; primary outcome: 30-day mortality; compared outcomes between high- and low-risk patients; for each severity score, pooled sensitivity and specificity are reported	858 abstracts reviewed; 60 articles selected as potentially eligible; 15 studies met criteria; 2 excluded owing to insufficient patient numbers or insufficient data reported; PSI: 10 studies with 3,972 patients; pooled results: PSI I through III: mortality 0.2%, PSI IV and V: mortality 10.1%; for PSI I through III, pooled sensitivity was 92% (95% CI 64% to 100%) and pooled specificity was 90% (95% CI 89 to 91); AUC was 0.92 (SE 0.03); CRB65: 4 studies with 1,648 patients; pooled results: score 0, 0% mortality; score 1, 0.5%; score 2, 6.3%; score 3, 13.2%; score 4, no patients; using CRB-65 >1 to define hospital admission, pooled sensitivity was 81% (95% CI 54% to 96%) and pooled specificity was 91% (95% CI 90% to 93%) AUC 0.91 (SE 0.05); CURB-65: 2 studies; no meta-analysis performed owing to low number of studies	Included prospective and retrospective studies; only included English-language articles; small number of studies for CRB-65 and CURB-65; limited numbers of adverse outcomes led to instability with CIs

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Atlas et al[18] (1998)	III for Q1	Single-center prospective cohort study, results compared with historical controls; program evaluation of treating patients at home with PNA; nonrandomized interventional study including patients who do not receive the intervention	Eligible patients: 18 to 84 y, new infiltrate on CXR, symptoms consistent with PNA; excluded if immunocompromised, pregnant, homeless, history of intravenous drug use, unable to receive oral meds, or on long-term oxygen therapy; intervention provided physicians with PSI and corresponding mortality risk; enrolled patients had access to home nurse visits and the antibiotic clarithromycin; observed 166 prospectively enrolled low-risk patients and compared their results with those of 147 low risk historical controls from the prior year	Percentage treated as outpatient increased from 42% to 57%, but more patients in the intervention group were subsequently admitted (0% vs 9%); trend toward more patients in the intervention group receiving all their care in the outpatient setting but not statistically significant	No adjustment for baseline severity or propensity to admit; industry sponsored

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Marrie et al[19] (2000)	III for Q1	Randomized trial of 19 hospitals to pathway (n=9) vs no pathway/conventional (n=10); 1,743 patients for 6 mo (January to June 1998); pathway: used the PSI to guide admission decision, but the pathway includes administration of Levaquin, and practice guidelines, in addition to the PSI	Outcome: reduction in number of BDPM and outcome: reduction in percentage of low-risk patients admitted for CAP; exclusion criteria: immunocompromised, shock, pregnant/nursing, chronic renal failure; used PSI <90 to recommend discharge; 2 independent investigators evaluated outcomes and were unaware of the treatment assignment	Pathway associated with a 1.7-day reduction in BDPM, 18% decrease in admission of low-risk patients (31% vs 49%), 1.7 fewer days of IV antibiotics (4.6 vs 6.3), and more likely to receive a single class of antibiotic (64% vs 27%); pathway use had no adverse effects on quality of life, admission to the ICU (0.3%), mortality (–0.1%), readmission to hospital (0.7%), or complications (0.6%)	Sample size was justified on the basis of a difference in BDPM (10 in each arm, so did not meet power analysis); additionally, lost 1 hospital randomized to the pathway; unclear whether it was the PSI or other aspects of the pathway (Levaquin or practice guidelines) that led to the outcomes; Canadian hospitals only; different health care system than US (limits applicability to US)
Yealy et al[20] (2005)	III for Q1	Cluster randomized trial; 32 EDs randomized to low-, moderate-, or high-intensity process improvement for CAP care, using the PSI as a tool for risk stratification	Prospective enrollment; retrospective outcome assessment by telephone, medical record review, or both; no blinding; safety outcome: 30-day mortality	3,615 patients enrolled; only 1 patient died in the low-risk group treated as an outpatient	Indirectly applicable to question because this study evaluated process improvement, which included PSI as a part; generalizable because it included 32 EDs from 2 states, using an effectiveness paradigm

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Julián-Jiménez et al[21] (2013)	III for Q1	Prospective, pre-post analysis of implementation of the management of CAP in ED clinical practice guidelines from 2008; single-center tertiary care center in Spain; consecutive adult sample of n=400	"Appropriate" decision re: admission/discharge based on PSI and biomarkers; early and appropriate antibiotics, total antibiotic and IV therapy times, time to clinical stabilization, length of hospital stay, and inhospital mortality	35% of the pre group had an "inappropriate" destination in 35% of the time compared with 3.6% in the post group; inappropriate discharges in PSI groups 4 and 5 decreased from 35.5% in the pre to 2% in the post group, and in PSI groups 1 through 3 it decreased from 44% to 5.1%; the number of readmissions to the ED after initial discharge was lower in the post group (22, or 28.6%, to 3, or 4.5%)	Baseline differences: the prior use of antibiotics and proportion with severe sepsis was 9% and 7.2%, more common in the post group; definition of what is appropriate or inappropriate is defined by the guideline, so it is circular reasoning to state that the disposition was appropriate or not; however, there does seem to be a difference in the proportion of readmissions to the ED, which was lower in the post group; it is a single-center study using circular reasoning
Lim et al[23] (2003)	III for Q1	Multicenter retrospective cohort study, academic, European	Patients admitted for CAP; evaluated CURB prediction rule to predict 30-day mortality; derived and validated CURB-65 rule	N=1,068 (derivation 718, validation 214) with 9% mortality; CURB ≥2: sensitivity 74% (95% CI 68% to 80%), specificity 73% (95% CI 67% to 79%); CURB-65 ≥2: sensitivity 80%, specificity 61%	Secondary analysis of prospectively collected data; cohort includes only inpatients; it was basically an internal validation because they divided up the data set into 80% used for derivation and 20% for the validation; no description is provided about the chart review in gathering the predictor variables

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Dean et al[25] (2016)	III for Q1	Multicenter retrospective cohort study; 7 Intermountain Healthcare Hospitals in Utah; two 12-mo periods: December 2009 through November 2010, December 2011 through November 2012	Investigated pleural effusions at first encounter and subsequent clinical outcomes; enrolled patients >18 y evaluated in EDs and receiving diagnosis of PNA (*ICD-9* codes 480 through 487.0) or respiratory failure or sepsis (*ICD-9* codes 518.x and 038.x) as the primary diagnosis, with PNA secondary; PNA severity calculated with eCURB; PaO2 calculated with proxies for missing arterial blood gas data; other missing data imputed with modified iterative-scheme algorithms; excluded if no radiographic evidence for PNA, if diagnosis of aspiration, or if immunocompromised; severity-adjusted association of both unilateral and bilateral effusions with comorbid illnesses modeled using hospital admission, length of stay, and mortality as outcomes; hierarchical logistic and linear regression models used to determine performance characteristics	N=4,771 with PNA; of these, 690 (14.5%) had a pleural effusion; patients with pleural effusion at presentation were more likely to be admitted to the hospital (77% vs 57%; *P*<.001) and stayed longer in the hospital (median 2.8 vs 1.3 days; *P*<.001); if initially not admitted to the hospital from the ED, patients were more likely to be secondarily admitted within 7 days (17% vs 5%; *P*<.001); patients with pleural effusion had a greater likelihood of mortality (OR 2.6; 95% CI 2.0 to 3.5; *P*<.001), controlling for eCURB and the PaO2/FiO2 ratio; additionally controlling for the Elixhauser comorbidity score decreased the OR to 2.4	Unclear how presence of effusion influenced disposition decisions

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Jones et al[26] (2014)	III for Q1	Multicenter retrospective cohort study; 7 Intermountain Healthcare Hospitals in Utah from December 2009 to December 2010	The study aimed to (1) compare their admission criteria to A-DROP ≥2 and CURB-65 ≥2 for their agreement with actual hospital admission and potential to reduce hospital admissions and outpatient failures (secondary hospitalization or death), and (2) compare eCURB, CURB-65, and A-DROP for their ability to predict 30-day mortality for ED patients with CAP versus health care–associated PNA; enrolled patients >18 y with primary diagnosis of PNA, or respiratory failure/sepsis primary with PNA secondary; excluded for aspiration, immunocompromised, or absence of radiographic evidence for PNA; the CURB-65, eCURB, and A-DROP scores were tested for their ability to predict 30-day mortality using logistic regression and by calculating the AUC; we also used the AUC to compare admission criteria to CURB-65 ≥2 and A-DROP ≥2 for accuracy in predicting inpatient versus outpatient triage	N=2,308 patients, admission rate 57%, 30-day mortality 6.1%, 7-day secondary hospitalization 5.8%, and outpatient failure rate 6.4%; admission criteria predicted hospital admission with an AUC of 0.77 compared with 0.73 for CURB-65 ≥2 and 0.78 for A-DROP ≥2; hypothetical 100% concordance with admission criteria decreased the hospitalization rate to 52% and reduced the outpatient failure rate to 3.9%, slightly better than A-DROP ≥2 (54% and 4.3%) and CURB-65 ≥2 (49% and 5.1%); among the 30-day mortality predictors, eCURB was superior overall, with an AUC of 0.83 vs 0.79 for A-DROP, and 0.78 for CURB-65 (P<.001); there was no statistically significant difference in performance between A-DROP and CURB-65 (P=.97)	Unclear how investigators used other rules to affect disposition decisions; unclear whether manual abstraction was undertaken blinded to disposition and 30-day mortality; study required hierarchical modeling to account for clustering by hospital site

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Buising et al[28] (2006)	III for Q1	Prospective cohort study at a single urban center, Melbourne, Australia	Enrolled ED patients with diagnosed PNA; excluded if <18 y, history of immunosuppression, cystic fibrosis, hospital discharge in prior 2 wk; assessed PSI, CURB, CURB-65, Modified BTS severity score (2-step CURB), revised ATS score; the performance characteristics of the severity scores in predicting inhospital mortality, need for ICU admission and composite outcome of requiring either inotropic support or noninvasive or invasive ventilation within 48 h of presentation when no other cause for circulatory or respiratory failure was clinically evident; secondary analysis excluding patients >90 y, those from nursing homes, and those receiving palliative care	N=392 patients with CAP; of these, 26 (6.6%) required ICU admission, 37 (9.4%) died while in hospital, 48.4% of dead patients were >90 y or resided in a nursing home, or were considered to be unsuitable for aggressive treatment; PORT mortality prediction: class I, 0; class II, 0; class III, 2%; class IV, 8%; class V, 28%; excluded nursing home, >90 y, or palliative patients; sensitivity of the tools for mortality in the remaining patients was 18 of 19 patients (94.7%) for both PSI classes IV and V and for CURB; 17 of 19 patients (89.5%) for CURB-65; 100% for the modified BTS severity score, and 11 of 19 patients (57.8%) for the revised ATS score; 29 patients who died were not admitted to the ICU before death, 11 of whom were not in the group >90 y, from a nursing home, or identified as not for resuscitation within 24 h of presentation; the CURB, PSI classes IV and V, and modified BTS severity score tools all identified 10 of these 11 patients as “severe”; the rates of ICU admission in each of the PSI classes were class I, 0; class II, 2%; class III, 5%; class IV, 7%; and class V, 14%; the revised ATS score performed well in identifying patients requiring ICU admission, as did the modified BTS severity score, but CURB-65 had a sensitivity of only 57.7% for ICU admission; PSI classes IV and V and CURB had similar predictive values for this outcome of interest; for 8 patients who required ICU admission and were not admitted directly from the emergency department, 7 required transfer from the ward to the ICU within 24 h; both the PSI classes IV and V and the CURB definitions of severity correctly identified 7 of these 8 patients (1 patient was misclassified by both tools)	Scores may have been used to determine severity and disposition and ICU admission was an outcome leading to overestimation of performance owing to incorporation bias; only 35.9% of patients had arterial blood gas tested, limiting PSI scoring; unclear how missing data were handled; included cases of "clinical PNA"; some data were retrieved retrospectively

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Chalmers et al[31] (2011)	III for Q1	Meta-analysis of prospective and retrospective studies published between 1980 and October 2009	Objective to assess differences in performance between the PSI, CURB-65, and CRB-65, ATS risk scores in predicting ICU admission from CAP; all studies were considered eligible if they fulfilled the following criteria: original publications, inclusion of patients with CAP, radiographic confirmation of CAP and exclusion of non-CAP diagnoses, such as nonpneumonic exacerbation of COPD; calculation of severity score based on admission data; studies involving only outpatients were excluded; primary outcome was the frequency of ICU admission (during hospitalization for CAP or within 30 days of diagnosis) in patients meeting severity score criteria; surrogates of ICU admission, such as the receipt of mechanical ventilation or vasopressor support, were also collected; used PubMed and EMBASE; included all languages; excluded conference abstracts; 2 investigators	N=28 studies included in meta-analysis; 26 articles reported data on PSI and the prediction of ICU admission, reporting cohorts comprising 25,609 patients with 2,410 ICU admissions, giving a cumulative ICU admission rate of 9.4%; using a PSI ≥IV to determine ICU admission, the pooled sensitivity was 74.1% (95% CI 72.3% to 75.8%) and the pooled specificity 47.9% (95% CI 47.3% to 48.6%), with a positive LR of 1.48 (95% CI 1.38% to 1.59%) and a negative LR of 0.53 (95% CI 0.47 to 0.60); 11 articles reported data for CURB-65 and the prediction of ICU admission; these studies reported data on 11,602 patients with an event rate of 9.9% overall; using CURB-65 ≥3 to determine ICU admission, the pooled sensitivity was 48.8% (95% CI 45.9% to 51.7%) and the pooled specificity was 74.0% (95% CI 73.2% to 74.9%), with a positive LR of 1.70 (95% CI 1.36 to 2.11) and a negative LR of 0.72 (95% CI 0.60 to 0.86); the diagnostic OR was 2.85 (95% CI 2.17 to 3.74); using CURB-65 ≥4 to determine ICU admission, the pooled sensitivity was 28.9% (95% CI 22.5% to 35.9%) and the pooled specificity was 89.9% (95% CI 88.6% to 91.0%), with a positive LR of 2.09 (95% CI 1.12 to 3.90) and a negative LR of 0.86 (95% CI 0.68 to 1.09); 4 studies reported data for CRB-65 and ICU admission; data were available for only 3,096 patients with 271 events, giving a cumulative ICU admission rate of 8.8%; using a score of ≥3 to determine ICU admission, the pooled sensitivity was 41.7% (95% CI 35.8% to 47.8%) and the pooled	Inconsistent outcome use; significant heterogeneity in all analyses of discrimination; no sensitivity analysis was undertaken using higher-quality studies; incorporation bias from investigators using rules to determine disposition likely because these rules disseminated into common practice

Evidentiary Table (continued).

			independently assessed article eligibility and quality using modified Hayden criteria, tables included; pooled estimates for outcomes ratios, sensitivity, specificity, positive and negative LRs reported from random-effects models stratified by risk categories; heterogeneity assessed with Cochran's Q test and Higgins' I^2 test	specificity was 85.1% (95% CI 83.8% to 86.4%), with a positive LR of 3.0 (95% CI 1.44 to 6.25) and a negative LR of 0.69 (95% CI 0.57 to 0.84); 9 studies reported data on the 2001 ATS criteria; these studies contained 4,833 patients with an ICU admission rate of 16.4%; the pooled sensitivity was 66.7% (95% CI 63.3% to 70.0%) and the pooled specificity was 84.6% (95% CI 83.5% to 85.7%), with a positive LR of 7.05 (95% CI 4.39 to 11.3) and a negative LR of 0.34 (95% CI 0.26 to 0.44); 5 studies reported validation data for the 2007 IDSA/ATS criteria; the validation studies involved 6,488 patients with an ICU admission rate of 14.5%; the pooled sensitivity was 61.2% (95% CI 58% to 64.3%) and the pooled specificity was 88.6% (95% CI 87.7% to 89.4%), with a pooled positive LR of 6.2 (95% CI 3.3 to 11.7) and a pooled negative LR of 0.43 (95% CI 0.35 to 0.53); none of the scoring systems demonstrated a positive LR >10 or a negative LR <0.1 using any of the recognized cutoffs; patients in CURB-65 group 0 were at lowest risk of ICU admission, negative LR 0.14 (95% CI 0.06 to 0.34), whereas the 2001 ATS criteria had the highest, positive LR 7.05 (95% CI 4.39 to 11.3)	

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Liapikou et al[33] (2009)	III for Q1	Retrospective cohort study at single urban, academic medical center between 2000 and 2007	Adults with CAP admitted to hospital; outcome: ICU admission	N=2,102 (235 admitted to ICU); 2007 IDSA/ATS criteria for severe CAP: sensitivity 71%, specificity 88% for ICU admission; κ coefficient=0.45 between IDSA/ATS prediction and ICU admission	Retrospective, secondary analysis of earlier cohort study; creatinine >2 mg/dL imputed for blood urea nitrogen ≥20 mg/dL criterion; unclear external generalizability because this was a single-center study
Fukuyama et al[35] (2011)	III for Q1	Single-center prospective study at community hospital in Japan	Patients admitted for CAP; evaluated different clinical prediction rules to predict mechanical ventilation, septic shock, ICU admission, or inpatient mortality	N=505 with 6.5% inpatient mortality; España rule: sensitivity 97%, specificity 35%; PSI (IV and V): sensitivity 93%, specificity 31%; A-DROP: sensitivity 77%, specificity 60%; CURB-65: sensitivity 60%, specificity 69%; 2007 IDSA/ATS: sensitivity 87%, specificity 62%; SMART-COP: sensitivity 93%, specificity 45%	Outcome assessment was not blinded; cohort includes only inpatients and therefore may not generalize to ED population

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Chalmers et al[36] (2011)	III for Q1	Prospective observational study of consecutive adult patients with CAP admitted to National Health Service Lothian (Scotland, United Kingdom)	Cohort of PNA patients without major criteria for ICU admission but who were eligible for ICU admission if required; exclusion criteria included HAP, systemic immunosuppression, radiographic changes owing to lung cancer rather than PNA, HIV infection, solid organ transplant, and pulmonary TB or any obvious reason for ICU admission; no scoring systems were used to guide ICU admission decisions in the study hospitals; PSI, CURB-65, SCAP, SMART-COP, 2001 ATS minor criteria were calculated; outcomes: severe CAP, defined as definition of severe CAP; secondary outcome was all-cause 30-day mortality; calculated performance characteristics and AUC for ROCs	Of the 1,723 PNA patients identified, 1,625 lacked major criteria, and 1,062 had no contraindications to ICU admission (ie, do-not-resuscitate orders); overall 30-day mortality rate was 4.5%, and 7.6% of patients subsequently required ICU admission; of the patients admitted to the ICU, 86.4% required mechanical ventilation/vasopressor support during their admission, 207 patients (19.5%) met at least 3 2007 IDSA/ATS minor criteria with an AUC-ROC curve of 0.85 (95% CI 0.82 to 0.88) for prediction of mechanical ventilation/vasopressor support, 0.85 (95% CI 0.82 to 0.88) for prediction of ICU admission, and 0.78 (95% CI 0.74 to 0.82) for prediction of 30-day mortality; criteria were at least as equivalent to more established scoring systems	To calculate severity scores, missing data were assumed to be normal; <0.1% of data were missing for calculation of severity scores, and no values were missing for calculation of the 2007 IDSA/ATS criteria; none of the scoring systems achieved a positive LR of >10 or a negative LR of <0.1, which is regarded as providing robust prediction; none of the prediction tools achieved sensitivity or specificity of 100%; spectrum bias, given persons at highest risk were removed from the analysis; unclear study enrollment dates

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
España et al[38] (2006)	III for Q1	Single-center prospective cohort study in Spain between March 2000 and March 2004	Enrolled patients >18 y with a pulmonary infiltrate on CXR not known to be old and with symptoms consistent with PNA; excluded if immunocompromised; patients with an expected terminal event (defined as metastatic cancer, advanced dementia, or a disease or condition with a high likelihood of predicted fatality during the next 30 days) were included; from the β parameter obtained in the multivariate logistic regression models, a score was assigned to each predictive variable; assessed with a derivation and validation set; by adding up the points assigned to each predictive variable, a score was given to each patient, with a higher score corresponding to a higher likelihood of SCAP; retrospective, external validation cohort was formed with patients admitted to 4 other hospitals in the same health network	N=1,776; of these, 46 episodes were classified as an expected terminal event at diagnosis; 1,057 patients were randomly assigned to the derivation cohort and 719 to the internal validation cohort; the rate of SCAP among admitted patients was 11.5% in the derivation cohort, 9.8% in the internal validation cohort, and 12% in the external cohort; inhospital mortality was 9.1%, 8.2%, and 9.7%, respectively; in multivariate analyses, 8 independent predictive factors were correlated with SCAP: systolic blood pressure <90 mm Hg, arterial pH <7.30, respiratory rate >30 breaths/min, blood urea nitrogen >30 mg/dL, oxygen arterial pressure <54 mm Hg or PaO2/FiO2 <250 mm Hg, altered mental status, ≥80 y, and multilobar/bilateral lung infiltrates on radiographs; when applying a cutoff point of 10 or greater, prediction rule showed an AUC of 0.83 for the derivation cohort, 0.86 for internal validation cohort, and 0.72 for the external validation; both m-ATS and CURB-65 had low sensitivity (51.3% and 68.4%), whereas PSI risk classes IV and V and adjusted PSI demonstrated poor specificity (68.1% and 57.5%) for the derivation cohort, trend lessened in the validation cohorts	Unclear whether blinded to outcome assessments; unclear whether investigators used other rules for patient disposition (incorporation bias); unclear how missing data were handled, seemingly cases were dropped because most <5%; however, some as high as 40% for respiratory rate, may have affected results

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
España et al[39] (2010)	III for Q1	Multicenter retrospective cohort study in Spain	Included adult ED patients with CAP, the majority of whom were admitted; outcome: 30-day mortality; evaluated SCAP, PSI, and CURB-65 rules	Validation cohort: N=712 with 6.7% 30-day mortality; SCAP: AUC 0.75 (95% CI 0.68 to 0.81); CURB-65: AUC 0.73 (95% CI 0.66 to 0.80); PSI: AUC 0.79 (95% CI 0.74 to 0.85)	Predictor and outcome variables were not measured in blinded fashion; authors reported that study was prospective but did not provide sufficient details to support this claim

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Labarère et al[41] (2012)	III for Q1	Retrospective cohort study; secondary analysis of RCT at 6 facilities in Switzerland	Using original data from a prospective multicenter RCT study of CAP patients, external validation of the REA-ICU index in predicting early ICU admission and clinically relevant outcomes was undertaken; also examined predictive performance of PNA severity assessment tools and alternate clinical prediction models of SCAP requiring intensive care; included patients with a definite diagnosis of CAP, defined by at least 1 respiratory symptom plus at least 1 finding during auscultation or 1 sign of infection, along with a new infiltrate on CXR; ineligible if unable to give consent, severe dementia, active intravascular cardiac unit, immunosuppression, life-threatening medical comorbidities leading to possible imminent death (HAP or if hospitalized in prior 14 days), and patients with chronic infection necessitating antibiotic treatment	N=850 patients; 30-day ICU admission and mortality rates were 64 of 850 patients (7.5%) and 40 of 850 patients (4.7%); in validation sample, rates of early intensive respiratory or vasopressor support, 30-day ICU admission, and 30-day all-cause mortality were 1.5%, 1.8%, and 1.5% for patients assigned to REA-ICU risk class I and 20.7%, 31.0%, and 20.7% for patients assigned to REA-ICU risk class IV; the REA-ICU index yielded AUC higher than PSI and CURB-65 scores in predicting ICU admission and comparable to the 2007 IDSA/ATS minor severity criteria, SMART-COP, and SCAP (CURXO-80) in predicting early or 30-day outcome measures; REA-ICU index and other prediction models of severe CAP did not perform better than the PSI and CURB-65 scores in predicting 30-day mortality; none of the clinical prediction models of severe CAP and PNA severity assessment tools yielded a positive LR >10 or a negative LR <0.1 in predicting early ICU admissions; the NPVs ranged from 95% for the CURB-65 group 3 to 98% for the REA-ICU risk classes II through IV; the positive predictive values ranged from 9% for the PSI risk classes IV and V to 22% for the presence of 3 or more 2007 IDSA/ATS mi nor severity criteria	No clustering adjustment for data collected from 6 facilities; criteria for confusion not validated; no assessment of reliability of predictors; included patients with do-not-intubate orders; unclear how the REA-ICU and other predictors influenced disposition decisions; using ICU admission as a proxy for severe PNA may be confounded by other factors

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Marti et al[42] (2012)	II for Q1	Meta-analysis of prospective and retrospective studies	Assess performance of existing clinical prediction rules to identify in the ED patients with CAP requiring ICU admission or intensive treatment; prospective or retrospective studies evaluating clinical prediction rules in adult immunocompetent patients with CAP to predict the need for ICU admission, intensive treatment, or early mortality (<14 days); the evaluation had to be performed during the first 24 h after hospital admission; studies addressing specific patient subgroups based on cause or age were excluded; a prediction rule was defined as the combination of 2 or more clinical or biologic markers	N=36 articles included; identified 11 main severity scores based on 20 variables; sufficient data were available to perform a meta-analysis on 8; PSI: score of ≥IV had a pooled sensitivity of 75% and a specificity of 48%; a cutoff of V increased specificity to 84% and decreased sensitivity to 38%; ability of PSI to predict ICU admission was modest, with AUC 0.69; ability to predict an alternative definition of SCAP, including mortality, was superior, with a pooled sensitivity of 92.4% and specificity of 56.2% in 4 cohorts of 3,195 patients; CURB-65 was studied in 9 cohorts including 5,773 patients and 479 ICU admissions (8.3%); at score ≥3 pooled sensitivity was 56%, and specificity was 74%; performance of CURB-65 to predict ICU admission was similar to PSI with AUC of 0.69; ability to predict need for ventilation or vasopressors was studied in 3 publications including 2,951 patients, 264 requiring ICU; results were similar, with a pooled sensitivity of 57.2% and specificity of	Heterogeneity and pooling with random-effects models, sensitivity analyses done when there were sufficient data and numbers of articles; some data are reported and pooled even when heterogeneity was unable to be assessed; major heterogeneity limited validity of the meta-analysis; inclusion in the studied population of patients not at risk for ICU admission (patients with therapeutic limitations); and use as a predictor of a surrogate of the outcome (use of mechanical ventilation and vasopressors, which are universally delivered only in an ICU or intermediate care unit); ICU admission is influenced by ICU bed availability, local ICU admission policy, or subjectivity of the ICU specialists evaluation; some rules have been fully incorporated in specialist society recommendations, influencing ICU admission practices—incorporation bias; and overestimation of their accuracy

Evidentiary Table (continued).

				77.2%; CRB-65: 2 studies included 2,078 patients and 122 ICU patients (5.8%) measured ability of CRB-65 to predict ICU admission; for score ≥3 pooled sensitivity was 34% and specificity was 91%; CURB: ability to predict ICU admission was studied in 4 cohorts of 1,418 patients and 161 ICU admissions (12.1%); pooled sensitivity of CURB ≥2 to predict ICU admission was 76.8% and specificity was 68.6%; 2001 ATS: consists of 2 major (mechanical ventilation or shock) and 3 minor criteria (BP <90 mm Hg, PaO2/FiO2 <250 mm Hg, and multilobar involvement on CXR); the rule is considered positive in the presence of 1 major or 2 minor criteria; identified 8 studies including 7,116 patients with 908 ICU admissions (12.8%); the pooled sensitivity was 69.5%, and specificity was 90.1%; pooled AUC could not be calculated owing to insufficient data; pooled sensitivity was 52.7% and specificity was 95.1%; 2007 ATS/IDSA consists of 2 major (mechanical ventilation or shock) and 9 minor criteria; rule is positive in presence of 1 major or 3 minor criteria; 5	

Evidentiary Table (continued).

				publications evaluated; 2 studies of 2,400 patients and 266 ICU patients (11%) validated the original rule to predict ICU admission; pooled sensitivity was 84% and specificity was 78%; 4 studies evaluated the performance of minor criteria in a total of 6,412 patients including 650 ICU patients (10.1%); pooled sensitivity was 57%, and specificity was 90%; SMART-COP: pooled sensitivity to predict the need for vasopressors or mechanical ventilation was 79% and specificity was 68%; 2 studies evaluated this rule to predict ICU admission, with a pooled sensitivity of 79% and specificity of 64% on 1,567 patients including 112 ICU admissions (7.1%); SCAP score pooled performance of this rule on 3 cohorts totaling 3,402 patients (SCAP, 9%) to predict a composite definition of SCAP (inhospital death, mechanical ventilation, or shock) was 92% for sensitivity and 64% for specificity; pooled performance of the SCAP score to predict ICU admission in 2 recent cohorts was similar in terms of sensitivity (94%) but lower for specificity (46%)	

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Sharp et al[45] (2016)	III for Q1	Multicenter retrospective cohort study at 14 Kaiser Permanente EDs in Southern California from July 2009 to June 2012	Report the accuracy of CURB-65 at predicting 30-day mortality for groups of ED patients who were discharged or hospitalized; the primary outcome was 30-day all-cause mortality; eligible if >18 y with primary diagnosis of PNA or primary diagnosis of respiratory failure or sepsis with PNA as secondary; excluded if diagnosis of health care–associated PNA, hospitalized in prior 30 days, or immunocompromised; performance characteristics reported with AUC, *c* statistics, sensitivity analyses	N=21,183 with diagnosis of CAP; 7,952 (37.5%) resulted in ED discharge and 13,231 (62.5%) resulted in admission; for all ED CAP encounters (admitted and discharged), the *c* statistic, describing the accuracy of CURB-65 to predict 30-day mortality, was 0.76 (95% CI 0.75 to 0.77); a CURB-65 threshold of ≥1 (N=13,920), a low-risk score that has previously been suggested to support outpatient management, was 92.8% sensitive and 38.0% specific for identifying patients who died within 30 days; CURB-65 was more accurate among discharged patients (*c* statistic=0.86; 95% CI 0.82 to 0.91) than admitted patients (*c* statistic=0.69; 95% CI 0.67 to 0.71); CURB-65 threshold of ≥1 demonstrated higher sensitivity (94.8% vs 92.7%) and specificity (62.4% vs 22.3%) among those discharged (N=6,982) than for those admitted (N=6,938)	Rules have been fully incorporated in specialist society recommendations, perhaps influencing admission practices and treatment decisions leading to incorporation bias and overestimation of accuracy; models failed to account for clustering; missing data were assumed normal or abnormal in lieu of multiple imputation

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Chen and Li[46] (2015)	III for Q1	Prospective cohort study from January 2012 to May 2014 at a single academic urban center ED in China with approximately 250,000 ED visits per year	Objective: investigate the predictive performance of lactate, CURB-65, and a combination of lactate and CURB-65 for mortality, hospitalization, and ICU admission in PNA patients in the ED; lactate and CURB-65 were defined to have 3 risk classes: low, moderate, and high; the CURB-65 risk category thresholds matched those proposed in the original study: low (CURB-65 ≤1), moderate (CURB-65 =2), and high risk (CURB-65 ≥3); lactate risk classes were defined as follows: low risk (lactate <2 mmol/L), moderate risk (2 to 4 mmol/L), and high risk (>4 mmol/L); the cohort was then separated into 3 risk groups according to the combination of lactate and CURB-65 (LAC-CURB-65): patients with 2 low risks, patients with any moderate risk, and those with a high risk; the 28-day mortality, hospitalization, and ICU admission were compared among the 3 groups; logistic regression models used to determine AUCs and performance characteristics for each risk category and outcome	N=1,641 patients; 861 (53%) were hospitalized (38% to a general ward, 15% to the ICU), whereas the remaining 780 (47%) were treated as outpatients or observed in the ED; 547 of 1,641 patients (33%) died within 28 days; lactate and CURB-65 were higher in patients who died, were hospitalized, or were admitted to the ICU compared with patients who were not (P<.001); lactate and CURB-65 independently predicted outcomes; the performance of lactate in predicting 28-day mortality, hospitalization, and ICU admission was higher than that of CURB-65 (P<.01); for LAC-CURB-65, patients at low or moderate risk had mortality rates of 2% and 14%, respectively, and hospitalization rates of 15% and 40%, respectively, whereas none were admitted to ICU; patients at high risk had the highest mortality (52%), hospitalization (70%), and ICU admission rates (27%)	Investigators were not blinded to CURB score or outcomes; incorporation bias likely influenced hospital disposition decisions; mortality rates high (33%), leading to spectrum bias

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Christ-Crain et al[47] (2007)	III for Q1	Prospective cohort study at a single academic urban center ED in Basel, Switzerland, from November 2003 through February 2005	Primary study objective was to determine antibiotic duration based on PCT guidance; a secondary outcome was assessment of prognostic factors and biomarkers in CAP; patients >18 y with suspected CAP enrolled; excluded cystic fibrosis, active TB, and severely immunocompromised; PCT, CRP levels, leukocyte count, clinical variables, and the PSI were measured; proADM levels were measured with a new immunoassay; CAP defined by presence of 1 or more of the following: cough, sputum production, dyspnea, temperature >38.0°C (100.4°F), rales, WBC $>10\times10^9$/L or $<4\times10^9$/L, infiltrate on CXR; patients were followed for 7 wk on average in the original study; this substudy validated the use of cortisol in the risk stratification of CAP; the major outcome measures were PSI and survival	N=302 patients; total cortisol and free cortisol, but not CRP or leukocytes, increased with increasing severity of CAP according to the PSI ($P<.001$); total cortisol and free cortisol levels on presentation in patients who died during follow-up were significantly higher compared with levels in survivors; AUC was 0.76 (95% CI 0.70 to 0.81) for total cortisol and 0.69 (95% CI 0.63 to 0.74) for free cortisol; this was similar to the AUC of the PSI 0.76 (95% CI 0.70 to 0.81) and better compared with CRP, PCT, or leukocytes; in univariate analysis, the predictive potential of total cortisol equaled the prognostic power of PSI for mortality	No mention of blinded outcome assessment; unclear whether results from laboratory tests and PSI scoring affected disposition decisions—incorporation bias; preplanned secondary analysis; unclear whether antibiotic duration was affected by proADM levels; unclear how missing data were handled; funded by the assay company

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Christ-Crain et al[48] (2008)	III for Q1	Prospective cohort study at a single academic urban center ED in Basel, Switzerland, from November 2003 to February 2005	Primary study objective was to determine antibiotic duration based on PCT guidance; a secondary outcome was assessment of prognostic factors and biomarkers in CAP; patients >18 y with suspected CAP enrolled; excluded: cystic fibrosis, active pulmonary TB, HAP, and the severely immunocompromised; PCT, CRP levels, leukocyte count, clinical variables, and the PSI were measured; proADM levels were measured with a new immunoassay; CAP defined by presence of 1 or more of the following: cough, sputum production, dyspnea, temperature >38.0°C (100.4°F), rales, WBC $>10\times10^9$/L or $<4\times10^9$/L, infiltrate on CXR; patients were followed for 7 wk on average in the original study; the major outcome measures were PSI and survival; this substudy validated the use of B-type natriuretic peptide in the risk stratification of CAP	N=302 patients enrolled; patients with mild CAP defined as PSI class I, II, or III had significantly lower B-type natriuretic peptide levels compared with patients with severe CAP defined as PSI class IV and V (P=.02); the combination of B-type natriuretic peptide and the PSI significantly improved the prognostic accuracy of the PSI alone (AUC 0.78 vs 0.71; P=.02)	No mention of blinded outcome assessment; unclear whether results from laboratory tests and PSI scoring affected disposition decisions—incorporation bias; preplanned secondary analysis; unclear whether antibiotic duration was affected by proADM levels; unclear how missing data were handled; funded by the assay company

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Lee et al[49] (2011)	III for Q1	Prospective cohort study at single academic center in Korea between April 2008 and March 2010	Determine association of commonly used biochemical markers, such as albumin and CRP, with mortality and the prognostic performance of these markers combined with the PSI for mortality and adverse outcomes in patients with CAP; hypothesized albumin and CRP would be associated with 28-day mortality and improve mortality prediction in hospitalized patients with CAP; eligible patients >18 y and had a diagnosis of CAP; excluded if transferred from another hospital, discharged from a hospital in prior 10 days, prior diagnosis of PNA within 30 days, active pulmonary TB, HIV, or chronically immunosuppressed; primary outcome 28-day mortality; secondary outcomes, vasopressor use, mechanical ventilation, ICU admission; logistic regression and Cox proportional hazards models used	N=424 patients; 28-day mortality was 13.7%; in patients who were categorized into the same PSI class, especially PSI classes IV and V, mortality was higher in those who had low serum albumin (<3.3 mg/dL) or high CRP (≥14.3 mg/dL) than in patients who had high serum albumin (≥3.3 mg/dL) or low CRP (<14.3 mg/dL); in patients who had albumin less than 3.3 mg/dL, mortality was significantly higher than in those with albumin 3.3 mg/dL or more (22.1% vs 6.8%; $P<.05$); mortality was higher in patients with CRP 14.3 mg/dL or more than in those with CRP less than 14.3 mg/dL (20.2% vs 9.2%; $P<.05$); the AUC to predict 28-day mortality was 0.66 (95% CI 0.60 to 0.72) for albumin, 0.61 (95% CI 0.55 to 0.68) for CRP, and 0.76 (95% CI 0.71 to 0.81) for PSI; the AUCs significantly increased when albumin or CRP was added to PSI; for ICU admission, vasopressor use, or need for mechanical ventilation, albumin had an additive role with PSI (AUC 0.75), but CRP did not; however, the combination of albumin, CRP, and PSI increased AUC significantly (0.76) compared with PSI alone (0.70)	Secondary analysis of protocol implementation study for PSI; unclear how PSI and other tests affected disposition decisions—incorporation bias; unclear how cut points were selected; by trial and error, theory, or optimization algorithms

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Golcuk et al[50] (2015)	III for Q1	Prospective observational study at a single center in Turkey between September 2013 and July 2014	Investigated whether MPV is correlated with the CURB-65 and whether a combination of the CURB-65 score with MPV could better predict the 28-day mortality in patients with CAP; patients included if >18 y, hospitalized, or discharged from the ED with CAP; excluded those immunosuppressed, pregnant, readmissions, HAP, aspiration PNA, TB; CAP defined as new pulmonary infiltrates on chest imaging with symptoms consistent with PNA, including cough with or without sputum, temperature >38.0°C (100.4° F) or <36.0ºC (96.8° F), pleuritic chest pain not acquired in a hospital, or all 3; PNA severity assessed with CURB-65; survival analysis models used	A total of 174 patients (mean age 66.7 y [standard deviation 15.8 y]; 66.1% men) with CAP were enrolled in this study; all-cause mortality at the 28-day follow-up evaluation was 16.1%; a significant and inverse correlation between MPV and CURB-65 score was found (R=–0.58; *P*=.001); optimal MPV cutoff for predicting 28-day mortality at ED admission was 8.55 fL, with a 75% sensitivity and a 75.3% specificity; CURB-65 prediction of 28-day mortality, AUC 0.81 (95% CI 0.74 to 0.89); CURB-65 and MPV 0.89 (95% CI 0.81 to 0.93)	Unclear how missing data were handled; unclear whether investigators were blinded to MPV results or study purpose; unclear how CURB-65 affected baseline disposition decisions

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Christ-Crain et al[51] (2006)	III for Q1	Prospective cohort study at a single academic urban center ED in Basel, Switzerland, from November 2003 through February 2005	Primary study objective was to determine antibiotic duration based on PCT guidance; a secondary outcome was assessment of prognostic factors and biomarkers in CAP; patients >18 y with suspected CAP enrolled; excluded: cystic fibrosis, active TB, HAP, and the severely immunocompromised; PCT, CRP levels, leukocyte count, clinical variables, and the PSI were measured; proADM levels were measured with a new immunoassay; CAP defined by presence of 1 or more of the following: cough, sputum production, dyspnea, temperature >38.0°C (100.4°F), rales, WBC >10 or $<4\times10^9$/L, infiltrate on CXR; patients were followed for 7 wk on average in the original study; this substudy validated the use of PCT in the risk stratification of CAP	N=302 patients; proADM levels, in contrast to CRP and leukocyte count, increased with increasing severity of CAP, classified according to the PSI score (ANOVA, $P<.001$); in patients who died during follow-up, proADM levels on admission were significantly higher compared with levels in survivors, 2.1 nmol/L (95% CI 1.5 to 3.0) versus 1.0 nmol/L (95% CI 0.6 to 1.6), $P<.001$; in ROC analysis for survival, the AUC for proADM was 0.76 (95% CI 0.71 to 0.81), which was significantly higher compared with PCT ($P=.004$), CRP ($P<.001$), and total leukocyte count ($P=.001$) and similar to the AUC of the PSI (0.73; $P=.54$); a clinical model including the PSI and proADM increased the prognostic accuracy to predict failure compared with a model relying on the PSI alone (AUC 0.77; 95% CI 0.70 to 0.84; $P=.03$)	No mention of blinded outcome assessment; preplanned secondary analysis; unclear whether antibiotic duration was affected by proADM levels; unclear how missing data were handled; funded by the assay company

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Courtais et al[52] (2013)	III for Q1	Prospective cohort single-center ED in France from June 2009 to July 2010	Evaluated the prognostic value of midregional proADM in ED patients with a diagnosis of CAP and analyzed the added value of proADM as a risk stratification tool in comparison with other biomarkers and clinical severity scores; evaluated proADM, CRP and PCT, along with the PSI score in consecutive CAP patients; primary outcome 30-day mortality; performance characteristics assessed with ROC curve analysis, logistic regression, and reclassification metrics for all patients and for patients with high PSI scores	N=109; 9 patients died within 30 days; a 0.58 correlation between proADM and PSI was found; PSI and proADM levels were significantly predictive of risk of death; in patients with PSI class IV and V (score >90), proADM levels significantly predicted risk of death (OR 4.68; 95% CI 1.66 to 20.22; *P*=.012), whereas PSI score did not (*P*=.12); AUC was higher for proADM than for PSI score, AUC 0.81 (95% CI 0.65 to 0.96) and 0.66 (95% CI 0.44 to 0.89), respectively; reclassification analysis revealed that combination of PSI and proADM allows a better risk assessment than PSI alone (*P*=.001)	Industry sponsored; too few outcomes to support results or the analyses that were undertaken

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Huang et al[59] (2009)	III for Q1	Multicenter prospective cohort study of 28 teaching and nonteaching hospital EDs in southwestern Pennsylvania, Connecticut, southern Michigan, and western Tennessee between November 2001 and November 2003	Objective: describe the pattern of MR-proADM in a broad CAP cohort, confirm its prognostic role, and compare its performance to PCT; eligible: ≥18 y with clinical and radiologic diagnosis of PNA; excluded if transferred from another hospital, discharged from hospital in prior 10 days, diagnosis of PNA within 30 days, receiving long-term mechanical ventilation, history of cystic fibrosis, active pulmonary TB, having a known positive HIV antibody titer, having alcoholism with evidence of end-organ damage, admitted for palliative care, incarcerated, or pregnant; prospectively assessed severity of illness using PSI; calculated CURB-65 retrospectively using altered mental status or a new change in Glasgow Coma Scale score as proxy measures for confusion; primary outcome was 30-day mortality; secondary outcomes included 90-day mortality, length of stay, and ICU admission; survival analysis models	N=1,653 patients; MR-proADM levels consistently increased with PSI class and 30-day mortality (P<.001); MR-proADM had a higher AUC for 30-day mortality than PCT (0.76 vs 0.65, respectively; P<.001); adding MR-proADM to the PSI in all subjects minimally improved performance; among low-risk subjects (PSI classes I to III), mortality was low and did not differ by MR-proADM quartile; however, among high-risk subjects (PSI classes IV and V; N=546), subjects in the highest MR-proADM quartile (N=232; 42%) had higher 30-day mortality than those in MR-proADM quartiles 1 to 3 (23% vs 9%, respectively; P<.0001); similar results were seen with CURB-65	Only 71% of patients in the larger study cohort had MR-proADM levels tested; secondary analysis of larger study; unclear whether investigators blinded to PCT results during hospitalization, although likely, given methods; unclear whether mortality results were known by data abstractors; multiple comparisons and stratifications were done without any adjustments; industry sponsored

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
España et al[60] (2015)	III for Q1	Single-center prospective cohort study in Spain from July 2008 to July 2009	Prospective observational study in a teaching hospital among patients with CAP; in addition to collecting data for the prognostic scales, samples were taken at the ED for assessing PCT, CRP, and proADM levels; compared the prognostic accuracy of biomarkers with severity scores to predict PNA-related complications, using the AUC; classification and regression trees analysis used to derive prediction rules; investigators were blinded to laboratory results when making disposition decisions but may have used prediction scores	N=491 patients with CAP; 256 admitted to the hospital and 235 treated as outpatients; admitted patients had higher biomarker levels than outpatients (P<.001); the SCAP score and proADM level had the best AUCs for predicting PNA-related complications (0.83 and 0.84, respectively); considering SCAP score plus proADM level, the AUC increased significantly to 0.88; SCAP score class 0 or 1 with a proADM level <0.5 ng/mL was the best indicator for selecting patients for outpatient care	Unclear how physicians used risk scores to influence disposition decisions; unclear how missing data were handled; industry sponsored

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Huang et al[61] (2008)	III for Q1	Multicenter prospective cohort study of 28 teaching and nonteaching hospital EDs in southwestern Pennsylvania, Connecticut, southern Michigan, and western Tennessee between November 2001 and November 2003	Described the pattern of PCT in CAP, and determined whether PCT provides prognostic information beyond PSI and CURB-65; eligible: ≥18 y with clinical and radiologic diagnosis of PNA; excluded if transferred from another hospital, discharged from hospital in prior 10 days, diagnosis of PNA within 30 days, receiving long-term mechanical ventilation, history of cystic fibrosis, active pulmonary TB, with a known positive HIV antibody titer, having alcoholism with evidence of end-organ damage, admitted for palliative care, incarcerated, or pregnant; prospectively assessed severity of illness using PSI; calculated CURB-65 retrospectively using altered mental status or a new change in Glasgow Coma Scale score as proxy measures for confusion; stratified PCT into 4 tiers: tier I <0.1, tier II ≥0.1 to <0.25, tier III ≥0.25 to <0.5, and tier IV ≥0.5 ng/mL; primary outcome was 30-day mortality; secondary outcomes included 90-day mortality, length of stay, and ICU admission; survival analysis models	N=1,651; PCT levels: tier I 32.8%, tier II 21.6%, tier III 10.2%, tier IV 35.4%; used alone, PCT test characteristics: specificity 35% to 64%, sensitivity 87% to 92%, positive LR 1.41, and negative LR 0.22; adding PCT to PSI in all subjects minimally improved performance; adding PCT to low-risk PSI subjects (classes I through III) provided no additional information; subjects in PCT tier I had low 30-day mortality regardless of clinical risk, including those in higher-risk classes (1.5% vs 1.6% for those in PSI classes I through III vs classes IV and V); among high-risk PSI subjects (classes IV and V), 126 of 546 patients (23.1%) were in PCT tier I, and the negative LR of PCT tier I was 0.09; PCT tier I was also associated with lower burden of other adverse outcomes; similar results were seen with CURB-65 stratification; results were similar with CURB-65: 181 of 825 patients (21.9%) of CURB-65 group 2 and 3 subjects had a PCT level in tier I, and mortality was 4 of 181 patients (2.2%) vs 89 of 644 patients (13.8%) for subjects with PCT levels in tier I vs tiers II through IV (P<.0001), yielding a negative LR for a low PCT of 0.18	Secondary analysis of larger study; only 71% had PCT levels tested; unclear whether investigators blinded to PCT results during hospitalization, although likely, given methods; unclear whether mortality results were known by data abstractors; multiple comparisons and stratifications were done without any adjustments; industry sponsored

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Self et al[62] (2016)	III for Q1	Multicenter prospective cohort study CDC EPIC between January 2010 and June 2012	Evaluate the association of a single serum PCT measurement at hospital presentation with the need for IRVS during the first 72 h among adults hospitalized with CAP; also evaluated the additive value of PCT when used in conjunction with several existing PNA severity scores; logistic regression models, AUC analysis, performance characteristics with CIs reported	N=1,770 patients; 115 patients (6.5%) required IRVS within 72 h of hospital presentation; higher PCT concentration correlated with increasing PNA severity at presentation as measured by the number of ATS minor criteria present, PSI score, and SMART-COP score; addition of PCT to each of PNA severity score models increased the AUC curves; area under the AUC curve for the ATS minor criteria alone was 0.75 and improved to 0.78 when PCT was added; addition of PCT represented a significant improvement in model fit for IRVS for each severity score (LR test $P<.01$ for each model); PCT concentration had larger contribution to predicting IRVS than any of the individual ATS minor criteria; patients classified as low risk by the ATS minor criteria (<3 criteria present) had a 4.7% (95% CI 3.7% to 5.7%) risk of IRVS; PCT <0.05 ng/mL corresponded to a 2.4% (95% CI 1.7% to 3.4%) IRVS risk, whereas a PCT concentration of 10 ng/mL corresponded to a 12% (95% CI 6.4% to 21.3%) risk; without considering PCT, patients classified as high risk by the ATS minor criteria (≥3 criteria present) had a 29.7% (95% CI 21.7% to 37.6%) risk of IRVS; within this high-risk subgroup by ATS minor criteria, PCT <0.05 ng/mL was associated with a 13.2% (95% CI 9.3% to 18.5%) IRVS risk, whereas a PCT concentration of 10 ng/mL corresponded to a 36.2% (95% CI 25.0% to 49.1%) risk; similar results were found with PSI and SMART-COP	Secondary analysis of prospective trial, one of many; rules have been fully incorporated in specialist society recommendations, perhaps influencing ICU admission practices and decisions to start vasopressors or intubate, leading to incorporation bias and overestimation of accuracy; models failed to account for clustering

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Schuetz et al[64] (2017)	II for Q2	Cochrane meta-analysis using individual patient-level data from 26 RCTs in 12 countries and 6,708 patients; 14 of the trials were in the ED and included 3,805 patients	PCT to initiate or stop antibiotics in lower respiratory tract infections; primary outcomes were all-cause mortality or 30-day treatment failure; secondary outcomes included duration of antibiotic therapy	Mortality lower in PCT-guided therapy: 286 of 3,336 PCT guided (8.6%) compared with 336 of 3,372 (10.0%) (adjusted OR 0.83; 95% CI 0.70 to 0.99); no difference in treatment failure of PCT-guided therapy (23% vs 24.9%); lower antibiotic use (2.43 days less) in PCT-guided groups	No significant difference in outcomes when analysis was limited to ED trials; heterogeneity of trials; half of trials were funded by Thermo Fisher, the manufacturer of the PCT assay; some caution needs to be used in interpreting the OR because the absolute mortality reduction was 1.4%; because physicians used PCT for decisionmaking, there was no blinding to the treatment allocation group; lack of high-quality criterion standard for bacterial infection
Schuetz et al[65] (2018)	II for Q2	Meta-analysis using patient-level data and Cochrane methodology; 26 RCTs in 12 countries and 6,708 patients; 14 of the trials were in the ED including 3,805 patients	PCT to initiate or stop antibiotics in lower respiratory tract infections; outcomes were treatment failure or death; secondary outcomes included duration of antibiotic therapy	Mortality lower in PCT-guided therapy (adjusted OR 0.83; 95% CI 0.70 to 0.99); no difference in treatment failure of PCT-guided therapy (23% vs 24.9%); lower antibiotic use (2.43 days less) in PCT-guided groups; when only including ED-based trial, the finding of mortality benefit was no longer statistically significant	This is the same meta-analysis as the 2017 Cochrane review: same 26 articles and same 6,708 patients

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Huang et al[66] (2018)	II for Q2	Multicenter clinical trial; 14 emergency departments in US	Adult patients with acute lower respiratory infection but for whom there was uncertainty about use of antibiotics; 1:1 randomization between use of PCT assay and guideline to aid interpretation vs usual care; outcomes: total antibiotic exposure; composite of adverse outcomes that could be attributed to withholding antibiotics	N=1,656 (826 PCT group; 830 usual care); PCT levels received by clinicians in 95.9% of the PCT group and 2.2% of the usual care group; no difference in antibiotic days between groups (mean 4.2 vs 4.3 days, respectively; difference=–0.05, 95% CI –0.6 to 0.5; *P*=.87); no difference in adverse outcomes between groups (11.7% vs 13.1%, respectively; difference=–1.5%, 95% CI –4.6% to 1.7%; *P*<.001 for noninferiority)	Did not directly address whether antibiotics could be safely withheld on the basis of low PCT; approximately 20% lost to 30-day follow-up
Müller et al[90] (2007)	III for Q2	545 patients with suspected lower respiratory tract infection; combined patient cohorts from 2 previous prospective RCTs; preplanned post hoc analysis	Comparison of PCT-driven antibiotics versus standard of care; additionally, PCT, CRP, and WBC evaluated as tools to diagnose and prognosticate CAP outcomes	PCT and hsCRP, AUC 0.92 (95% CI 0.89 to 0.94), improved the AUC for diagnosing PNA compared with physical examination alone, AUC 0.79 (95% CI 0.75 to 0.83); PCT was better, AUC 0.88 (95% CI 0.84 to 0.93), compared with hsCRP, AUC 0.76 (95% CI 0.69 to 0.83); PCT >0.1 g/L had a 90% sensitivity and 59% specificity; hsCRP >40 mg/L had an 89% sensitivity and 52% specificity; PCT and CRP performed best in diagnosis and risk stratification of CAP	Single-center study; combined 2 studies with slightly different recruitment inclusion and exclusion criteria; pathogen identified by culture in only 26% of patients, leaving criterion standard in question; polymerase chain reaction was not performed routinely for *Streptococcus pneumoniae* and not performed at all for *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*; lack of high-quality criterion standard for bacterial infection

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Rainer et al[91] (2009)	III for Q2	Single-center prospective case-control study of 561 adult patients with lower respiratory tract infection	Measured the CRP to neopterin ratio to predict bacterial infection; suspected PNA diagnosed clinically based on 2 or more of the following clinical signs and symptoms: temperature ≥38°C (100.4°F), chills, tachypnea ≥24 breaths/min, tachycardia ≥100 beats/min, pleuritic chest pain, cough, sputum production, dyspnea, chest signs	CRP elevated above 10 nmol/L in 94.9% of patients with bacterial cause; CRP also higher in patients with bacterial PNA vs viral PNA (177.5 vs 33.1 mg/L; $P<.0001$); neopterin levels higher in viral than in bacterial PNA (25.2 vs 13.3 nmol/L; $P<.0001$) CRP to neopterin ratio was higher in bacterial vs viral PNA (12.5 vs 1.2 mg/nmol; $P<.0001$). CRP to neopterin ratio ≤0.06 had 100% sensitivity and 3.7% specificity and CRP to neopterin ratio of >40 had a sensitivity of 9.4% and specificity of 100%	Single-center study; specialized test (neopterin) unclear utility in the ED; lack of high-quality criterion standard for bacterial infection; assumed no coexistence of viral and bacterial infection

ATS, American Thoracic Society; *AUC*, area under the curve; *BDPM*, bed days per patient management; *BTS*, British Thoracic Society; *CAP*, community-acquired pneumonia; *CI*, confidence interval; *CRP*, C-reactive protein; *CXR*, chest radiograph; *dL*, deciliter; *eCURB*, electronic version of CURB-65; *fL*, femtoliter; *h*, hour; *HAP*, hospital-acquired pneumonia; *hsCRP*, high-sensitivity C-reactive protein; *IDSA*, Infectious Diseases Society of America; *IRVS*, invasive respiratory or ventilator support; *L*, liter; *LR*, likelihood ratio; *mg*, milligram; *mL*, milliliter; *MPV*, mean platelet volume; *MR-ProADM*, midregional pro-adrenomedullin; *ng*, nanogram; *NPV*, negative predictive value; *nmol*, nanomole; *OR*, odds ratio; *PCT*, procalcitonin; *PNA*, pneumonia; *ProADM*, pro-adrenomedullin; *PSI*, Pneumonia Severity Index; *RCT*, randomized controlled trial; *REI-ICU*, risk of early admission to the ICU; *ROC*, receiver operating characteristic; *SCAP*, severe community-acquired pneumonia; *TB*, tuberculosis; *US*, United States; *WBC*, white blood cell; *y*, year; *μg*, microgram.