

Diagnosis and Treatment of Adults with Community-acquired Pneumonia

An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America: Executive Summary

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Background: This document provides evidence-based clinical practice guidelines on the management of adult patients with community-acquired pneumonia.

Methods: A multidisciplinary panel conducted pragmatic systematic reviews of the relevant research and applied Grading of Recommendations, Assessment, Development, and Evaluation methodology for clinical recommendations.

Results: The panel addressed 16 specific areas for recommendations spanning questions of diagnostic testing, determination of site of care, selection of initial empiric antibiotic therapy, and subsequent management

decisions. Although some recommendations remain unchanged from the 2007 guideline, the availability of results from new therapeutic trials and epidemiological investigations led to revised recommendations for empiric treatment strategies and additional management decisions.

Conclusions: The panel formulated and provided the rationale for recommendations on selected diagnostic and treatment strategies for adult patients with community-acquired pneumonia.

Keywords: community-acquired pneumonia; pneumonia; patient management

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Introduction

In the 10 years since the last American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) community-acquired pneumonia (CAP) guideline (1), there have been changes in the process for guideline development, as well as generation of new clinical data. ATS and IDSA agreed on moving from the narrative style of previous documents to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) format. We thus developed this updated CAP guideline as a series of questions answered from available evidence in an “is option A better than option B” format using the Patient or Population, Intervention, Comparison, Outcome (PICO) framework (2).

This guideline addresses the clinical entity of pneumonia that is acquired outside of the hospital setting by adults who do not have an immunocompromising condition. Antibiotic recommendations are based on selecting agents effective against the major

treatable bacterial causes of CAP. As bacterial pathogens often coexist with viruses and there is no current diagnostic test accurate enough or fast enough to determine that CAP is due solely to a virus at the time of presentation (*see below*), our recommendations are to initially treat empirically for possible bacterial infection or coinfection. In addition, the emergence of multidrug-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, require separate recommendations when the risk of each of these pathogens is elevated. We acknowledge that other multidrug-resistant Enterobacteriaceae can cause CAP, including organisms producing extended-spectrum β -lactamase, but we do not discuss them separately because they are much less common and are effectively covered by the strategies presented for *P. aeruginosa*. Therefore, throughout this document when discussing *P. aeruginosa* we are also referring to other similar multiresistant gram-negative bacteria.

We have maintained the convention of separate recommendations on the basis of the severity of illness. Although historically site of care (outpatient, inpatient general ward, ICU) has served as a severity surrogate, decisions about site of care may be based on considerations other than severity and can vary widely between hospitals and practice sites. We have therefore chosen to use the IDSA/ATS CAP severity criteria that have been validated and define severe CAP as present in patients with either one major criterion or three or more minor criteria (Table 1).

This guideline reaffirms many recommendations from the 2007 statement. However, new evidence and a new process have led to significant changes, which are summarized in Table 2.

Methods

The guideline development methodology and how conflict of interest was managed

are presented in the online supplement. We followed the GRADE standards for evaluating the evidence for each PICO and assigned a quality of evidence rating of high, moderate, low, or very low. On the basis of the quality of evidence, recommendations were assigned as strong or conditional. Recommendations that were based on low or very low quality of evidence and not believed to represent standards of care were labeled as conditional recommendations. Statements in favor of strong recommendations begin with the words “We recommend . . .”; statements in favor of conditional recommendations begin with the words “We suggest” Although we specified pairwise PICO questions for all antibiotic options in the outpatient and inpatient settings, we summarized the recommendations using lists of treatment options, in no preferred order, rather than retain the PICO format for this section.

Recommendations

Question 1: In Adults with CAP, Should Gram Stain and Culture of Lower Respiratory Secretions Be Obtained at the Time of Diagnosis?

Recommendation. We recommend not obtaining sputum Gram stain and culture routinely in adults with CAP managed in the outpatient setting (strong recommendation, very low quality of evidence).

We recommend obtaining pretreatment Gram stain and culture of respiratory secretions in adults with CAP managed in the hospital setting who:

1. are classified as severe CAP (*see* Table 1), especially if they are intubated (strong recommendation, very low quality of evidence); or
2.
 - a. are being empirically treated for MRSA or *P. aeruginosa* (strong recommendation, very low quality of evidence); or
 - b. were previously infected with MRSA or *P. aeruginosa*, especially those with prior respiratory tract infection (conditional recommendation, very low quality of evidence); or
 - c. were hospitalized and received parenteral antibiotics, whether during the hospitalization event or not, in

the last 90 days (conditional recommendation, very low quality of evidence).

Rationale for the recommendation. In balancing the lack of evidence supporting routine sputum culture with the desire for improved antimicrobial stewardship, the committee voted to continue the stance of previous guidelines in recommending neither for nor against routinely obtaining sputum Gram stain and culture in all adults with CAP managed in the hospital setting. Whether to culture patients or not should be determined by individual clinicians on the basis of clinical presentation, local etiological considerations, and local antimicrobial stewardship processes.

The committee identified two situations in which we recommend sputum Gram stain and culture: in hospitalized patients with severe CAP, and when strong risk factors for MRSA and *P. aeruginosa* are identified, unless local etiological data have already shown these pathogens are very infrequently identified in patients with CAP. Patients who have severe CAP requiring intubation should have lower respiratory tract samples, such as endotracheal aspirates, sent for Gram stain and culture promptly after intubation, particularly as these patients may be more likely to have pneumonia due to MRSA or *P. aeruginosa* and endotracheal aspirates have a better yield of microbiological organisms than sputum culture (3).

We recommend obtaining sputum for Gram stain and culture in situations when risk factors for MRSA or *P. aeruginosa* are present, both when initial empiric therapy is expanded to cover these pathogens and when it is not expanded. In the former case, negative microbiological test results may be used to deescalate therapy, and in the latter case, positive microbiological test results may be used to adjust therapy. As discussed below, although there are numerous studies identifying individual risk factors for MRSA and *P. aeruginosa*, many of these associations are weak and vary across sites. The most consistently strong risk factor to consider is prior infection with either MRSA or *P. aeruginosa*. In addition, hospitalization and treatment with parenteral antibiotics in the last 90 days is associated with an increased risk of these pathogens, and so we recommend sputum culture in this situation. These recommendations are not based on high-grade evidence but reflect the committee's

desire to improve antibiotic use as well as improve clinicians' understanding of their local pathogen prevalences and resistance patterns, which we believe are key to selecting appropriate empiric antibiotic therapy.

Question 2: In Adults with CAP, Should Blood Cultures Be Obtained at the Time of Diagnosis?

Recommendation. We recommend not obtaining blood cultures in adults with CAP managed in the outpatient setting (strong recommendation, very low quality of evidence).

We suggest not routinely obtaining blood cultures in adults with CAP managed in the hospital setting (conditional recommendation, very low quality of evidence).

We recommend obtaining pretreatment blood cultures in adults with CAP managed in the hospital setting who:

1. are classified as severe CAP (*see* Table 1) (strong recommendation, very low quality of evidence); or
2.
 - a. are being empirically treated for MRSA or *P. aeruginosa* (strong recommendation, very low quality of evidence); or
 - b. were previously infected with MRSA or *P. aeruginosa*, especially those with prior respiratory tract infection (conditional recommendation, very low quality of evidence); or
 - c. were hospitalized and received parenteral antibiotics, whether during the hospitalization event or not, in the last 90 days (conditional recommendation, very low quality of evidence).

Rationale for the recommendation. Although additional diagnostic information could improve the quality of treatment decisions, support for routine collection of blood cultures is reduced by the low quality of studies demonstrating clinical benefit. Routinely obtaining blood cultures may generate false-positive results that lead to unnecessary antibiotic use and increased length of stay.

In severe CAP, delay in covering less-common pathogens can have serious consequences. Therefore, the potential benefit of blood cultures is much larger when results can be returned within 24 to 48 hours. The rationale for the recommendation for blood cultures in the setting of risk factors for MRSA

Table 1. 2007 Infectious Diseases Society of America/American Thoracic Society Criteria for Defining Severe Community-acquired Pneumonia

Validated definition includes either one major criterion or three or more minor criteria

Minor criteria

Respiratory rate ≥ 30 breaths/min
 $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 250
 Multilobar infiltrates
 Confusion/disorientation
 Uremia (blood urea nitrogen level ≥ 20 mg/dl)
 Leukopenia* (white blood cell count $< 4,000$ cells/ μl)
 Thrombocytopenia (platelet count $< 100,000/\mu\text{l}$)
 Hypothermia (core temperature $< 36^\circ\text{C}$)
 Hypotension requiring aggressive fluid resuscitation

Major criteria

Septic shock with need for vasopressors
 Respiratory failure requiring mechanical ventilation

*Due to infection alone (i.e., not chemotherapy induced).

and *P. aeruginosa* is the same as for sputum culture.

Question 3: In Adults with CAP, Should *Legionella* and Pneumococcal Urinary Antigen Testing Be Performed at the Time of Diagnosis?

Recommendation. We suggest not routinely testing urine for pneumococcal antigen in adults with CAP (conditional recommendation, low quality of evidence), except in adults with severe CAP (conditional recommendation, low quality of evidence).

We suggest not routinely testing urine for *Legionella* antigen in adults with CAP (conditional recommendation, low quality of evidence), except

1. in cases where indicated by epidemiological factors, such as association with a *Legionella* outbreak or recent travel (conditional recommendation, low quality of evidence); or
2. in adults with severe CAP (see Table 1) (conditional recommendation, low quality of evidence).

We suggest testing for *Legionella* urinary antigen and collecting lower respiratory tract

secretions for *Legionella* culture on selective media or *Legionella* nucleic acid amplification testing in adults with severe CAP (conditional recommendation, low quality of evidence).

Rationale for the recommendation.

Randomized trials have failed to identify a benefit for urinary antigen testing for *Streptococcus pneumoniae* and *Legionella*. Concern has also been raised that narrowing therapy in response to positive urinary antigen tests could lead to increased risk of clinical relapse (4). In large observational studies, these diagnostic tests have been associated with reduction in mortality; therefore, we recommend testing in patients with severe disease. An increase in *Legionella* infections in the United States in the past decade highlights the importance of this diagnosis, especially among severely ill patients, particularly in the setting of potential outbreaks due to a common source, although most cases are not associated with a known outbreak and remain sporadic (5, 6).

Question 4: In Adults with CAP, Should a Respiratory Sample Be Tested for Influenza Virus at the Time of Diagnosis?

Recommendation. When influenza viruses are circulating in the community, we recommend testing for influenza with a rapid influenza molecular assay (i.e., influenza nucleic acid amplification test), which is preferred over a rapid influenza diagnostic test (i.e., antigen test) (strong recommendation, moderate quality of evidence).

Rationale for the recommendation. The benefits of antiviral therapy support testing of patients during periods of high influenza activity. During periods of low influenza activity, testing can be considered but may not be routinely performed. Of note, this testing recommendation has both therapeutic and infection-control implications in the hospital setting. Updated influenza testing recommendations are also available on the CDC website (<https://www.cdc.gov/flu/professionals/diagnosis/index.htm>).

Question 5: In Adults with CAP, Should Serum Procalcitonin plus Clinical Judgment versus Clinical Judgment Alone Be Used to Withhold Initiation of Antibiotic Treatment?

Recommendation. We recommend that empiric antibiotic therapy should be

initiated in adults with clinically suspected and radiographically confirmed CAP regardless of initial serum procalcitonin level (strong recommendation, moderate quality of evidence).

Rationale for the recommendation.

Procalcitonin has been used to guide initiation of antibiotics in patients with lower respiratory infections, but many of these studies are not restricted to patients with radiographically confirmed pneumonia. Some patients with low procalcitonin levels have CAP and have been safely treated without antibiotics (7), but these represent small subgroups, raising concerns about the safety of widely using such a strategy.

Question 6: Should a Clinical Prediction Rule for Prognosis plus Clinical Judgment versus Clinical Judgment Alone Be Used to Determine Inpatient versus Outpatient Treatment Location for Adults with CAP?

Recommendation. In addition to clinical judgement, we recommend that clinicians use a validated clinical prediction rule for prognosis, preferentially the Pneumonia Severity Index (PSI) (strong recommendation, moderate quality of evidence) over the CURB-65 (tool based on confusion, urea level, respiratory rate, blood pressure, and age ≥ 65) (conditional recommendation, low quality of evidence), to determine the need for hospitalization in adults diagnosed with CAP.

Rationale for the recommendation. Our recommendation to use the PSI as an adjunct to clinical judgment to guide the initial site of treatment is based on consistent evidence of the effectiveness and safety of this approach. Using a safe and effective decision aid to increase outpatient treatment of patients with CAP has potential to decrease unnecessary variability in admission rates, the high cost of inpatient pneumonia treatment (8, 9), and the risk of hospital-acquired complications. Providing a conditional recommendation to use CURB-65 considers its greater simplicity of use relative to the PSI despite the paucity of evidence regarding its effectiveness or safety.

Table 2. Differences between the 2019 and 2007 American Thoracic Society/Infectious Diseases Society of America Community-acquired Pneumonia Guidelines

Recommendation	2007 ATS/IDSA Guideline	2019 ATS/IDSA Guideline
Sputum culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or <i>Pseudomonas aeruginosa</i>
Blood culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or <i>P. aeruginosa</i>
Macrolide monotherapy	Strong recommendation for outpatients	Conditional recommendation for outpatients based on resistance levels
Use of procalcitonin	Not covered	Not recommended to determine need for initial antibacterial therapy
Use of corticosteroids	Not covered	Recommended not to use. May be considered in patients with refractory septic shock
Use of healthcare-associated pneumonia category	Accepted as introduced in the 2005 ATS/IDSA hospital-acquired and ventilator-associated pneumonia guidelines	Recommend abandoning this categorization. Emphasis on local epidemiology and validated risk factors to determine need for MRSA or <i>P. aeruginosa</i> coverage. Increased emphasis on deescalation of treatment if cultures are negative
Standard empiric therapy for severe CAP	β-Lactam/macrolide and β-lactam/fluoroquinolone combinations given equal weighting	Both accepted but stronger evidence in favor of β-lactam/macrolide combination
Routine use of follow-up chest imaging	Not addressed	Recommended not to obtain. Patients may be eligible for lung cancer screening, which should be performed as clinically indicated

Definition of abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*.

Question 7: Should a Clinical Prediction Rule for Prognosis plus Clinical Judgment versus Clinical Judgment Alone Be Used to Determine Inpatient General Medical versus Higher Levels of Inpatient Treatment Intensity (ICU, Step-Down, or Telemetry Unit) for Adults with CAP?

Recommendation. We recommend direct admission to an ICU for patients with hypotension requiring vasopressors or respiratory failure requiring mechanical ventilation (strong recommendation, low quality of evidence).

For patients not requiring vasopressors or mechanical ventilator support, we suggest using the IDSA/ATS 2007 minor severity criteria (Table 1) together with clinical judgment to guide the need for higher levels of treatment

intensity (conditional recommendation, low quality of evidence).

Rationale for the recommendation. Patients transferred to an ICU after admission to a hospital ward experience higher mortality than those directly admitted to the ICU from an emergency department (10–13). This higher mortality may in part be attributable to progressive pneumonia, but “mis-triage” of patients with unrecognized severe pneumonia may be a contributing factor (10). It seems unlikely that physician judgment alone would be equivalent to physician judgment together with a severity tool to guide the site-of-care decision. We recommend the 2007 IDSA/ATS severe CAP criteria over other published scores, because they are composed of readily available severity parameters and are more accurate than other available scores.

Question 8: In the Outpatient Setting, Which Antibiotics Are Recommended for Empiric Treatment of CAP in Adults?

Recommendation.

- For healthy outpatient adults without comorbidities listed below or risk factors for antibiotic resistant pathogens, we recommend (Table 3):
 - amoxicillin 1 g three times daily (strong recommendation, moderate quality of evidence), or
 - doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence), or
 - a macrolide (azithromycin 500 mg on first day then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin extended release 1,000 mg daily) only in areas with pneumococcal resistance to macrolides

Table 3. Initial Treatment Strategies for Outpatients with Community-acquired Pneumonia

	Standard Regimen
No comorbidities or risk factors for MRSA or <i>Pseudomonas aeruginosa</i> *	Amoxicillin or doxycycline or macrolide (if local pneumococcal resistance is <25%) [†]
With comorbidities [‡]	Combination therapy with amoxicillin/clavulanate or cephalosporin AND macrolide or doxycycline [§] OR monotherapy with respiratory fluoroquinolone

Definition of abbreviations: ER=extended release; MRSA=methicillin-resistant *Staphylococcus aureus*.

*Risk factors include prior respiratory isolation of MRSA or *P. aeruginosa* or recent hospitalization AND receipt of parenteral antibiotics (in the last 90 d).

[†]Amoxicillin 1 g three times daily, doxycycline 100 mg twice daily, azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, or clarithromycin ER 1,000 mg daily.

[‡]Comorbidities include chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia.

[§]Amoxicillin/clavulanate 500 mg/125 mg three times daily, amoxicillin/clavulanate 875 mg/125 mg twice daily, 2,000 mg/125 mg twice daily, cefpodoxime 200 mg twice daily, or cefuroxime 500 mg twice daily; AND azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, clarithromycin ER 1,000 mg daily, or doxycycline 100 mg twice daily.

^{||}Levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily.

<25% (conditional recommendation, moderate quality of evidence).

- For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia, we recommend (Table 3) (in no particular order of preference):

- Combination therapy:

- o amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); AND
- o macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation, moderate quality of evidence for combination therapy) or doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence for combination therapy); OR

- Monotherapy:

- o respiratory fluoroquinolone (levofloxacin 750 mg daily,

moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily) (strong recommendation, moderate quality of evidence).

Rationale for the recommendation. Given the paucity of randomized controlled trial (RCT) data in the outpatient setting, the committee considered all available evidence. The data included the few RCTs of outpatient CAP, observational studies, RCTs of inpatient CAP treatment, antimicrobial resistance data from surveillance programs, and data regarding antibiotic-related adverse events.

For patients without comorbidities that increase the risk for poor outcomes, the panel recommended amoxicillin 1 g every 8 hours or doxycycline 100 mg twice daily. The recommendation for amoxicillin was based on several studies that showed efficacy of this regimen for inpatient CAP despite presumed lack of coverage of this antibiotic for atypical organisms. This treatment also has a long track record of safety. The recommendation for doxycycline was based on limited clinical trial data, but a broad spectrum of action, including the most common relevant organisms. Some experts recommend that the first dose of oral

doxycycline be 200 mg, to achieve adequate serum levels more rapidly. There are no data assessing whether such an approach is associated with improved outcomes.

In a departure from the prior CAP guidelines, the panel did not give a strong recommendation for routine use of a macrolide antibiotic as monotherapy for outpatient CAP, even in patients without comorbidities. This was based on studies of macrolide failures in patients with macrolide-resistant *S. pneumoniae* (14, 15), in combination with a macrolide resistance rate of >30% among *S. pneumoniae* isolates in the United States, most of which is high-level resistance (16). However, in settings where macrolide resistance is documented to be low and there are contraindications to alternative therapies, a macrolide as monotherapy is a treatment option.

Patients with comorbidities should receive broader-spectrum treatment for two reasons. First, such patients are likely more vulnerable to poor outcomes if the initial empiric antibiotic regimen is inadequate. Second, many such patients have risk factors for antibiotic resistance by virtue of previous contact with the healthcare system and/or prior antibiotic exposure (see Recommendation 10) and are therefore recommended to receive broader-spectrum therapy to ensure adequate coverage. In addition to *Haemophilus influenzae* and *Moraxella catarrhalis* (both of which frequently produce β -lactamase), *S. aureus* and gram-negative bacilli are more common causes of CAP in patients with comorbidities, such as COPD.

Regimens recommended for patients with comorbidities include a β -lactam or cephalosporin in combination with either a macrolide or doxycycline. These combinations should effectively target macrolide- and doxycycline-resistant *S. pneumoniae* (as β -lactam resistance in *S. pneumoniae* remains less common), in addition to β -lactamase-producing strains of *H. influenzae*, many enteric gram-negative bacilli, most methicillin-susceptible *S. aureus*, and *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. The monotherapies listed also are effective against most common bacterial pathogens.

Both sets of treatment recommendations contain multiple antibiotic options without specifying a preference order. The choice between these options requires a risk-benefit assessment for each individual patient, weighing local epidemiological data

Table 4. Initial Treatment Strategies for Inpatients with Community-acquired Pneumonia by Level of Severity and Risk for Drug Resistance

	Standard Regimen	Prior Respiratory Isolation of MRSA	Prior Respiratory Isolation of <i>Pseudomonas aeruginosa</i>	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for MRSA	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for <i>P. aeruginosa</i>
Nonsevere inpatient pneumonia*	β-Lactam + macrolide [†] or respiratory fluoroquinolone [‡]	Add MRSA coverage [§] and obtain cultures/nasal PCR to allow deescalation or confirmation of need for continued therapy	Add coverage for <i>P. aeruginosa</i> and obtain cultures to allow deescalation or confirmation of need for continued therapy	Obtain cultures but withhold MRSA coverage unless culture results are positive. If rapid nasal PCR is available, withhold additional empiric therapy against MRSA if rapid testing is negative or add coverage if PCR is positive and obtain cultures	Obtain cultures but initiate coverage for <i>P. aeruginosa</i> only if culture results are positive
Severe inpatient pneumonia*	β-Lactam + macrolide [†] or β-lactam + fluoroquinolone [‡]	Add MRSA coverage [§] and obtain cultures/nasal PCR to allow deescalation or confirmation of need for continued therapy	Add coverage for <i>P. aeruginosa</i> and obtain cultures to allow deescalation or confirmation of need for continued therapy	Add MRSA coverage [§] and obtain nasal PCR and cultures to allow deescalation or confirmation of need for continued therapy	Add coverage for <i>P. aeruginosa</i> and obtain cultures to allow deescalation or confirmation of need for continued therapy

Definition of abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia.

*As defined by 2007 ATS/IDSA CAP severity criteria guidelines (see Table 1).

[†]Ampicillin + sulbactam 1.5–3 g every 6 hours, cefotaxime 1–2 g every 8 hours, ceftriaxone 1–2 g daily, or ceftaroline 600 mg every 12 hours AND azithromycin 500 mg daily or clarithromycin 500 mg twice daily.

[‡]Levofloxacin 750 mg daily or moxifloxacin 400 mg daily.

[§]Per the 2016 ATS/IDSA HAP/VAP guidelines: vancomycin (15 mg/kg every 12 h, adjust based on levels) or linezolid (600 mg every 12 h).

^{||}Per the 2016 ATS/IDSA HAP/VAP guidelines: piperacillin-tazobactam (4.5 g every 6 h), cefepime (2 g every 8 h), ceftazidime (2 g every 8 h), imipenem (500 mg every 6 h), meropenem (1 g every 8 h), or aztreonam (2 g every 8 h). Does not include coverage for extended-spectrum β-lactamase-producing Enterobacteriaceae, which should be considered only on the basis of patient or local microbiological data.

against specific risk factors that increase the risk of individual choices, such as documented β -lactam or macrolide allergy, cardiac arrhythmia (macrolides), vascular disease (fluoroquinolones), and history of infection with *Clostridium difficile*. In particular, despite the concern regarding adverse events associated with fluoroquinolones, the panel believed that fluoroquinolone therapy was justified for adults with comorbidities and CAP managed in the outpatient setting. Reasons included the performance of fluoroquinolones in numerous studies of outpatient CAP (17–22) and inpatient CAP (see inpatient CAP section), the very low resistance rates in common bacterial causes of CAP, their coverage of both typical and atypical organisms, their oral bioavailability, the convenience of monotherapy, and the relative rarity of serious adverse events related to their use. However, there have been increasing reports of adverse events related to fluoroquinolone use as summarized on the U.S. Food and Drug Administration website (23).

Of note, we adopt the convention of prior guidelines to recommend that patients with recent exposure to one class of antibiotics recommended above receive treatment with antibiotics from a different class, given increased risk for bacterial resistance to the initial treatment regimen. We also highlight that although patients with significant risk factors for CAP due to MRSA or *P. aeruginosa* (see Recommendation 11) are uncommonly managed in the outpatient setting, these patients may require antibiotics that include coverage for these pathogens.

Question 9: In the Inpatient Setting, Which Antibiotic Regimens Are Recommended for Empiric Treatment of CAP in Adults without Risk Factors for MRSA and *P. aeruginosa*?

Recommendation 9.1. In inpatient adults with nonsevere CAP without risk factors for MRSA or *P. aeruginosa* (see Recommendation 10), we recommend the following empiric treatment regimens (Table 4) (in no order of preference):

- combination therapy with a β -lactam (ampicillin + sulbactam 1.5–3 g every 6 h, cefotaxime 1–2 g every 8 h, ceftriaxone

1–2 g daily, or ceftaroline 600 mg every 12 h) and a macrolide (azithromycin 500 mg daily or clarithromycin 500 mg twice daily) (strong recommendation, high quality of evidence), or

- monotherapy with a respiratory fluoroquinolone (levofloxacin 750 mg daily, moxifloxacin 400 mg daily) (strong recommendation, high quality of evidence).

A third option for adults with CAP who have contraindications to both macrolides and fluoroquinolones is:

- combination therapy with a β -lactam (ampicillin + sulbactam, cefotaxime, ceftaroline, or ceftriaxone, doses as above) and doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence).

Rationale for the recommendation. As summarized in Table 4, the empiric antibiotic coverage recommendations for patients hospitalized with CAP remain aligned to cover the most likely pathogens causing CAP. There is a paucity of RCTs to favor the recommendation of combination β -lactam plus macrolide versus monotherapy with a respiratory fluoroquinolone versus combined therapy with β -lactam plus doxycycline.

Recommendation 9.2. In inpatient adults with severe CAP (see Table 1) without risk factors for MRSA or *P. aeruginosa*, we recommend (Table 4) (note specific agents and doses are the same as 9.1):

- a β -lactam plus a macrolide (strong recommendation, moderate quality of evidence), or
- a β -lactam plus a respiratory fluoroquinolone (strong recommendation, low quality of evidence).

Rationale for the recommendation. In the absence of data from clinical trials demonstrating the superiority of any specific regimen for patients with severe CAP, the committee considered epidemiological data for severe CAP pathogens and observational studies comparing different regimens. As a result, we recommend that combination therapy with a β -lactam plus a macrolide or a β -lactam plus a respiratory fluoroquinolone should be the treatment of choice for patients with severe CAP. Both fluoroquinolone monotherapy and the combination of β -lactam plus doxycycline have not been well studied in severe CAP

and are not recommended as empiric therapy for adults with severe CAP.

Question 10: In the Inpatient Setting, Should Patients with Suspected Aspiration Pneumonia Receive Additional Anaerobic Coverage beyond Standard Empiric Treatment for CAP?

Recommendation. We suggest not routinely adding anaerobic coverage for suspected aspiration pneumonia unless lung abscess or empyema is suspected (conditional recommendation, very low quality of evidence).

Rationale for the recommendation. Although older studies of patients with aspiration pneumonia showed high isolation rates of anaerobic organisms, more recent studies have shown that anaerobes are uncommon in patients hospitalized with suspected aspiration (24, 25). Increasing prevalence of antibiotic-resistant pathogens and complications of antibiotic use highlight the need for a treatment approach that avoids unnecessary use of antibiotics.

Question 11: In the Inpatient Setting, Should Adults with CAP and Risk Factors for MRSA or *P. aeruginosa* Be Treated with Extended-Spectrum Antibiotic Therapy Instead of Standard CAP Regimens?

Recommendation. We recommend abandoning use of the prior categorization of healthcare-associated pneumonia (HCAP) to guide selection of extended antibiotic coverage in adults with CAP (strong recommendation, moderate quality of evidence).

We recommend clinicians only cover empirically for MRSA or *P. aeruginosa* in adults with CAP if locally validated risk factors for either pathogen are present (strong recommendation, moderate quality of evidence). Empiric treatment options for MRSA include vancomycin (15 mg/kg every 12 h, adjust based on levels) or linezolid (600 mg every 12 h). Empiric treatment options for *P. aeruginosa* include piperacillin-tazobactam (4.5 g every 6 h), cefepime (2 g every 8 h), ceftazidime (2 g every 8 h), aztreonam (2 g every 8 h), meropenem (1 g every 8 h), or imipenem (500 mg every 6 h).

If clinicians are currently covering empirically for MRSA or *P. aeruginosa* in adults with CAP on the basis of published

risk factors but do not have local etiological data, we recommend continuing empiric coverage while obtaining culture data to establish if these pathogens are present to justify continued treatment for these pathogens after the first few days of empiric treatment (strong recommendation, low quality of evidence).

Rationale for the recommendation. Our approach to treating inpatient adults with CAP is summarized in Table 4. Our recommendation against using the former category of HCAP as a basis for selecting extended spectrum therapy is based on high-quality studies of patient outcomes. Although we understand that clinicians would prefer a simple rule that does not require incorporating site-specific data, the current evidence does not permit endorsement of a simple and accurate rule to determine which patients with CAP should be covered for MRSA and/or *P. aeruginosa*. However, the alternative approach to MRSA and *P. aeruginosa* that we propose as a replacement is not based on high-quality studies, because such studies do not exist. The lack of adequate outcome data and marked variation between sites in prevalence of MRSA and *P. aeruginosa* make generalizing any findings extremely difficult. We hope that future research will improve our understanding of this challenging clinical problem.

Our first principle was to maintain the distinction between severe and nonsevere pneumonia as per prior guidelines, because the risk of inadequate empiric antibiotic therapy is much greater in severe CAP. As noted previously, severity is defined by the degree of physiological impairment as classified by the IDSA/ATS 2007 criteria.

The second principle was that there is sufficient evidence that prior identification of MRSA or *P. aeruginosa* in the respiratory tract within the prior year predicts a very high risk of these pathogens being identified in patients presenting with CAP (26–31), and therefore these were sufficient indications to recommend blood and sputum cultures and empiric therapy for these pathogens in patients with CAP in addition to coverage for standard CAP pathogens, with deescalation at 48 hours if cultures are negative. We endorse the empiric treatment recommendations for MRSA and *P. aeruginosa* provided by the 2016 Clinical Practice Guideline from IDSA and ATS for the management of adults with

hospital-acquired and ventilator-associated pneumonia (32).

The major additional risk factors for MRSA and *P. aeruginosa* identified in the literature are hospitalization and parenteral antibiotic exposure in the last 90 days (30, 31, 33–45). In patients with recent hospitalization and exposure to parenteral antibiotics, we recommend microbiological testing without empiric extended-spectrum therapy for treatment of nonsevere CAP, and microbiological testing with extended-spectrum empiric therapy in addition to coverage for standard CAP pathogens for treatment of severe CAP, with deescalation at 48 hours if cultures are negative and the patient is improving.

The data supporting rapid MRSA nasal testing are robust (46, 47), and treatment for MRSA pneumonia can generally be withheld when the nasal swab is negative, especially in nonsevere CAP. However, the positive predictive value is not as high; therefore, when the nasal swab is positive, coverage for MRSA pneumonia should generally be initiated, but blood and sputum cultures should be sent and therapy deescalated if cultures are negative. However, this latter strategy of deescalation in the face of a positive nasal swab will vary depending on the severity of CAP and the local prevalence of MRSA as a pathogen.

Question 12: In the Inpatient Setting, Should Adults with CAP Be Treated with Corticosteroids?

Recommendation. We recommend not routinely using corticosteroids in adults with nonsevere CAP (strong recommendation, high quality of evidence).

We suggest not routinely using corticosteroids in adults with severe CAP (conditional recommendation, moderate quality of evidence).

We suggest not routinely using corticosteroids in adults with severe influenza pneumonia (conditional recommendation, low quality of evidence).

We endorse the Surviving Sepsis Campaign recommendations on the use of corticosteroids in patients with CAP and refractory septic shock (48).

Rationale for the recommendation. There are no data suggesting benefit of corticosteroids in patients with nonsevere CAP with respect to mortality or organ failure and only limited data in patients

with severe CAP. The risk of corticosteroids in the dose range up to 240 mg of hydrocortisone equivalent per day for a maximum of 7 days is predominantly hyperglycemia, although rehospitalization rates may also be higher (49), and more general concerns about greater complications in the following 30 to 90 days have been raised (50). At least one large trial (clinicaltrials.gov NCT01283009) has been completed but not reported and may further inform which subgroups of patients benefit from steroids. We also endorse the Surviving Sepsis Campaign recommendations on the use of steroids in patients with septic shock refractory to adequate fluid resuscitation and vasopressor support (48).

Of note, there is no intent that our recommendations would override clinically appropriate use of steroids for comorbid diseases, such as chronic obstructive pulmonary disease, asthma, and autoimmune diseases, where corticosteroids are supported as a component of treatment.

Question 13: In Adults with CAP Who Test Positive for Influenza, Should the Treatment Regimen Include Antiviral Therapy?

Recommendation. We recommend that antiinfluenza treatment, such as oseltamivir, be prescribed for adults with CAP who test positive for influenza in the inpatient setting, independent of duration of illness before diagnosis (strong recommendation, moderate quality of evidence).

We suggest that antiinfluenza treatment be prescribed for adults with CAP who test positive for influenza in the outpatient setting, independent of duration of illness before diagnosis (conditional recommendation, low quality of evidence).

Rationale for the recommendation. For inpatients, a substantial body of observational evidence suggests that giving antiinfluenza agents reduces mortality risk in adults with influenza infection. Although benefits are strongest when therapy is started within 48 hours of symptom onset, studies also support starting later (51). These data underlie our strong recommendation for using antiinfluenza agents for patients with CAP and influenza in the inpatient setting, consistent with the recently published

IDSA Influenza Clinical Practice Guideline (52).

Although we did not identify studies that specifically evaluated antiinfluenza agents for treating outpatients with CAP who test positive for influenza, we make the same recommendation as for inpatients, on the basis of the inpatient data and on outpatient data showing better time to resolution of symptoms and prevention of hospitalization among those with influenza but without pneumonia. Our recommendations are consistent with the IDSA influenza guidelines, which were recently released (52).

Question 14: In Adults with CAP Who Test Positive for Influenza, Should the Treatment Regimen Include Antibacterial Therapy?

Recommendation. We recommend that standard antibacterial treatment be initially prescribed for adults with clinical and radiographic evidence of CAP who test positive for influenza in the inpatient and outpatient settings (strong recommendation, low quality of evidence).

Rationale for the recommendation. The recommendation to routinely prescribe antibacterial agents in patients with influenza virus infection and pneumonia was based on evidence suggesting that bacterial coinfections are a common and serious complication of influenza, as well as the inability to exclude the presence of bacterial coinfection in a patient with CAP who has a positive test for influenza virus. Although low levels of biomarkers such as procalcitonin decrease the likelihood that patients have bacterial infections, these biomarkers do not completely rule out bacterial pneumonia in an individual patient with sufficient accuracy to justify initially withholding antibiotic therapy, especially among patients with severe CAP (53–55). We have provided a strong recommendation because of the significant risk of treatment failure in delaying appropriate antibacterial therapy in patients with CAP. However, in patients with CAP, a positive influenza test, no evidence of a bacterial pathogen (including a low procalcitonin level), and early clinical stability, consideration could be given to earlier

discontinuation of antibiotic treatment at 48 to 72 hours.

Question 15: In Outpatient and Inpatient Adults with CAP Who Are Improving, What Is the Appropriate Duration of Antibiotic Treatment?

Recommendation. We recommend that the duration of antibiotic therapy should be guided by a validated measure of clinical stability (resolution of vital sign abnormalities [heart rate, respiratory rate, blood pressure, oxygen saturation, and temperature], ability to eat, and normal mentation), and antibiotic therapy should be continued until the patient achieves stability and for no less than a total of 5 days (strong recommendation, moderate quality of evidence).

Rationale for the recommendation. As recent data supporting antibiotic administration for <5 days are scant, on a risk–benefit basis we recommend treating for a minimum of 5 days, even if the patient has reached clinical stability before 5 days. As most patients will achieve clinical stability within the first 48 to 72 hours, a total duration of therapy of 5 days will be appropriate for most patients. In switching from parenteral to oral antibiotics, either the same agent or the same drug class should be used.

We acknowledge that most studies in support of 5 days of antibiotic therapy include patients without severe CAP, but we believe these results apply to patients with severe CAP and without infectious complications. We believe that the duration of therapy for CAP due to suspected or proven MRSA or *P. aeruginosa* should be 7 days, in agreement with the recent HAP/VAP guidelines (32).

Question 16: In Adults with CAP Who Are Improving, Should Follow-up Chest Imaging Be Obtained?

Recommendation. In adults with CAP whose symptoms have resolved within 5 to 7 days, we suggest not routinely obtaining follow-up chest imaging (conditional recommendation, low quality of evidence).

Rationale for the recommendation. Available data suggest the positive yield from repeat imaging ranges from 0.2% to 5.0%; however, many patients with new

abnormalities in these studies meet criteria for lung cancer screening among current or past smokers (56).

Conclusions

Recommendations to help clinicians optimize therapy for their patients with CAP have been revised in light of new data. Methods of quality improvement are critical to the implementation of guideline recommendations. It remains disappointing how few key clinical questions have been studied adequately enough to allow for strong recommendations regarding the standard of care. We hope that the research priorities outlined in this document will prompt new investigations addressing key knowledge gaps.

Despite substantial concern over the rise of antibiotic-resistant pathogens, most patients with CAP can be adequately treated with regimens that have been used for multiple decades. It is also true that the subset of patients with CAP who have significant comorbidities and frequent contact with healthcare settings and antibiotics is increasing, and, in some settings, the rates of infection with MRSA or *P. aeruginosa* are high enough to warrant empiric treatment.

Unfortunately, microbiological testing has yet to deliver fast, accurate, and affordable testing that results in proven benefit for patients with CAP in terms of more rapid delivery of targeted therapy or safe deescalation of unnecessary therapy. Exceptions include rapid testing for MRSA and influenza. Until we have such widely available (and affordable) tests, therapy for many or most patients with CAP will remain empiric. Therefore, clinicians need to be aware of the spectrum of local pathogens, especially if they care for patients at a center where infection with antibiotic-resistant pathogens such as MRSA and *P. aeruginosa* are more common.

A difference between this guideline and previous ones is that we have significantly increased the proportion of patients in whom we recommend routinely obtaining respiratory tract samples for microbiologic studies. This decision is largely based on a desire to correct the overuse of anti-MRSA and antipseudomonal therapy that has occurred since the introduction of the HCAP classification (which we recommend

abandoning) rather than high-quality evidence. We expect this change will generate significant research to prove or disprove the value of this approach. As it is not possible to create a “one size fits all” schema for empiric therapy for CAP, clinicians must validate any approach taking into account their local spectrum and frequency of resistant pathogens, which is another driver for

recommending increased testing. We similarly expect our move against endorsing monotherapy with macrolides, which is based on population resistance data rather than high-quality clinical studies, will generate future outcomes studies comparing different treatment strategies.

We hope that clinicians and researchers will find this guideline useful,

but the recommendations included here do not obviate the need for clinical assessment and knowledge to ensure each individual patient receives appropriate and timely care. However, this guideline delineates minimum clinical standards that are achievable and will help drive the best patient outcomes on the basis of currently available data. ■

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