CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will suspect influenza as a cause of community-acquired pneumonia during influenza season

SARAH HAESSLER, MD
Division of Infectious Diseases, Baystate Medical Center; Assistant Professor of Medicine, Tufts University School of Medicine, Springfield, MA

JENNIFER J. SCHIMMEL, MD
Division of Infectious Diseases, Baystate Medical Center; Assistant Professor of Medicine, Tufts University School of Medicine, Springfield, MA

Managing community-acquired pneumonia during flu season

ABSTRACT

The clinical findings of influenza overlap those of community-acquired bacterial pneumonia (CABP), and influenza infection can be complicated by bacterial infections. Reviewed here are the epidemiology, pathophysiology, diagnosis, and management of community-acquired pneumonia (CAP) with special emphasis on considerations during influenza season.

KEY POINTS

Especially during flu season, clinicians should consider influenza in patients with respiratory symptoms.

The diagnosis of CAP is based primarily on clinical factors: a combination of signs and symptoms such as cough, fever, chills, sputum production, dyspnea, pleuritic pain, tachypnea, tachycardia, hypoxemia, consolidation or rales on auscultation, and a new infiltrate on chest imaging.

Empiric outpatient treatment of a previously healthy patient with CABP should include either a macrolide or doxycycline. A fluoroquinolone or beta-lactam plus a macrolide should be used for patients with comorbid conditions.

Several indices have been validated for use in deciding on inpatient vs outpatient treatment and whether a patient with pneumonia should be admitted to an intensive care unit.

doi:10.3949/ccjm.79a.11108

General internists need to be able to recognize community-acquired pneumonia (CAP) so that diagnostic and therapeutic interventions can be initiated promptly. It is also important to understand the most likely and possible causes of CAP so that appropriate initial antimicrobial therapy can be chosen. Especially during flu season, influenza can present as CAP and should be included in the differential diagnosis.

When managing a patient with CAP, the internist must decide which level of care, diagnostic tests, antimicrobial agents, and follow-up plans are needed. These topics will be reviewed in this article.

TWO TERMS TO REMEMBER

- **CAP** refers to pneumonia acquired outside a health care facility. It can be either bacterial or viral.
- **CABP** (community-acquired bacterial pneumonia) refers only to those cases caused by bacterial pathogens.

NUMBERS AND TRENDS

In the United States, CAP is the number-one cause of death from infection and the sixth leading cause of death overall.[1] Each year, it is responsible for about 4.2 million outpatient visits, more than 60,000 deaths, and more than $17 billion in health care expenses.[2]

Community-acquired bacterial pneumonia: Common, serious

In a population-based US study in 1991, the incidence of CABP requiring hospitalization was 266.8 per 100,000 people.[3]

Estimates of overall mortality in CABP vary depending on the severity of illness and comorbid conditions. A meta-analysis published in 1996 found the overall mortality rate to be 13.7%, with a range of 5.1% to 36.5% depending on severity.[4]

In hospitalized patients, mortality rates and length of hospital stay appear to be declining over time. Between 1993 and 2005, the age-adjusted mortality rate decreased from 8.9% to 4.1%, and the average length of stay decreased from 7.5 to 5.7 days, with an overall reduction in hospital cost.[5]

CABP is more prevalent in older people than in the general population, and it increases with age from 18.2 cases per 1,000 patient-years in patients 60 to 69 years to 52.3 cases per 1,000 patient-years in those older than 85 years.[6] Risk factors for pneumonia in the elderly include heart disease, chronic lung disease, immunosuppressive drugs, alcoholism, and increasing age.[7] Similar to the trend in the general population, the mortality rate in elderly CABP patients appears to be decreasing over time, possibly thanks to rising rates of pneumococcal and influenza vaccination.[8]

Mortality rates due to CAP seem to be declining, possibly thanks to vaccination

Among the general population, risk factors for developing CABP also include smoking, occupational dust exposure, history of childhood pneumonia, unemployment, and single marital status.[9] The incidence of CABP does not appear to be higher among pregnant women, although it is the most frequent cause of nonobstetric death in this population.[10]

The use of proton pump inhibitors may be an emerging risk factor for CABP.[11] Also, use of nonsteroidal anti-inflammatory drugs among patients with CABP is associated with a blunted inflammatory response as well as a higher risk of pleuropulmonary complications and a delay in presentation.[12]

Influenza is also common, potentially severe

Influenza is also very common and potentially severe. It can cause a spectrum of disease, from mild upper respiratory tract symptoms to severe viral pneumonia that can be life-threatening and complicated by respiratory failure and the acute respiratory distress syndrome (ARDS).

Influenza infection can also be complicated by subsequent bacterial pneumonia. However, the epidemiology of influenza infection differs from that of CABP in that influenza occurs seasonally.

In the United States, seasonal influenza causes 36,000 deaths and 200,000 hospitalizations annually.[13,14] As with CABP, the risk of death from influenza increases with age: it is 16 times greater in people age 85 and older than in those ages 65 to 69.[13]

During yearly seasonal epidemics, those at the highest risk of hospitalization and death are at the extremes of age. Risk factors for complicated influenza include heart disease, lung disease, diabetes, renal failure, rheumatologic conditions, dementia, and neurologic disease.[15,16] During the 2009 H1N1 influenza pandemic, unexpected severity was seen in previously healthy young adults as well as those with obesity, neurodegenerative disease, pregnancy, and asthma.[17]

PATHOGENS: TYPICAL, ATYPICAL, VIRAL

Identifying the etiologic organism in CAP is confounded by limitations in the available diagnostic tests and also by poor-quality specimens that often are contaminated with bacteria that colonize the upper airways. Given these caveats, the primary pathogens responsible for CAP broadly include typical bacterial pathogens, atypical bacterial pathogens, and viruses.

Typical bacterial pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, and, less commonly, a variety of aerobic and anaerobic gram-negative rods including *Pseudomonas aeruginosa*, *Acinetobacter* species, and *Klebsiella pneumoniae*.

Atypical bacterial pathogens include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species.[18]

Viruses implicated in adult CAP include influenza A and B, parainfluenza viruses, respiratory syncytial virus, and adenovirus.[19] More recently, human metapneumovirus has been described as a cause of adult CAP.[20]

Clues to uncommon microbes

Specific historic features or coexisting conditions that may suggest an uncommon microbiologic diagnosis include[21]:

- Recent travel to the southwestern United States or Southeast Asia
- Ill contacts
- Exposure to birds, bats, rabbits, or farm animals
- Alcoholism
- Chronic obstructive pulmonary disease
- Human immunodeficiency virus infection
- Structural lung disease
- Prolonged cough with whoop or posttussive vomiting
- Aspiration
- Bioterrorism.

In cases in which one or more of these conditions exist, CAP may also be caused by other agents not listed above, including *Mycobacterium tuberculosis*, oral anaerobes, atypical mycobacteria, *Histoplasma capsulatum*, *Chlamydophila psittaci*, *Francisella tularensis*, *Coxiella burnettii*, *Pneumocystis jiroveci*, *Cryptococcus*, *Aspergillus*, *Coccidioides*, *Hantavirus*, avian influenza, *Burkholderia pseudomallei*, severe acute respiratory syndrome virus, *Bordetella pertussis*, *Bacillus anthracis*, and *Yersinia pestis*.

HOW BACTERIA INVADE THE LUNGS

The pathophysiology of CABP involves both host defense and microbial virulence factors.

The airways are most commonly exposed to microbes by microaspiration of upper airway flora, although hematogenous seeding of the lungs in a bacteremic patient or contiguous spread of infection from an adjacent site can also occur.

Mucociliary clearance and the cough reflex are important initial defenses against infection and can be inhibited by neurologic diseases and conditions that impair the mucociliary mechanism. Mucosal immune cells, including macrophages and neutrophils, recognize invading pathogens and generate an antibody response.

Regulation of the host inflammatory response to infection depends on a complex interaction between immune cells, inflammatory cytokines (eg, tumor necrosis factor alpha, interleukin 1-beta, and interleukin 6), and anti-inflammatory cytokines such as interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor type I.[22]

The interaction and timing of the inflammatory and anti-inflammatory response are essential in manifesting an appropriate host response to infection. An inadequate inflammatory response can lead to sepsis and death, but an excessive, late anti-inflammatory response can lead to a systemic inflammatory response such as ARDS. Polymorphisms within the genes coding for these factors may explain the variation in severity of illness among patients with CABP.[23]

HOW INFLUENZA DOES ITS DAMAGE

There are three types of influenza virus: A, B, and C. Type A causes most human infections. The influenza A virus envelope comprises a lipid bilayer that contains the projecting glycoproteins hemagglutinin and neuraminidase. Influenza viruses are named on the basis of these proteins and are designated with an H and an N, respectively, each followed by a number referring to the subtype.

Influenza infection begins when the virus makes contact with the epithelium. Hemagglutinin binds to the host cell and allows viral entry, where it begins replication. Neuraminidase prevents viral aggregation and facilitates the release of virus from infected cells.[24]

Mature virions are released and spread to neighboring host cells; this process is associated with desquamation and inflammation of the airways, causing cough, rhinorrhea, and sore throat. Systemic symptoms are associated with the induction of interferon, which causes fever and myalgia.[25]

Recovery and immunity to influenza infection occurs through both humoral and cell-mediated immunity, with antibodies directed against the specific hemagglutinin and neuraminidase antigens of the infecting virus. Immunity wanes over time and with antigenic drift of circulating viruses, making the host susceptible to recurrent influenza infection.[24]

Typical pathogens in CAP: *S pneumoniae, H influenzae, S aureus, M catarrhalis*

Influenza is often complicated by bacterial superinfection

The influenza virus acts synergistically with certain bacteria to increase infectivity, and this may explain why influenza is often complicated by bacterial superinfection.

Mechanisms leading to bacterial superinfection include increased binding and inva-

sion of bacteria, increased viral replication, and modification of the host inflammatory response. Some *S aureus* strains produce a protease that directly activates influenza virus hemagglutinin; other bacteria can activate plasminogen to promote influenza replication. The resulting increase in proteases in host tissues promotes activation of influenza through cleavage of hemagglutinin.[26]

The influenza virus also causes damage to the airway epithelial layer, leading to increased exposure of the binding sites necessary for adherence of *S pneumoniae*.[27]

CLINICAL PRESENTATION OF COMMUNITY-ACQUIRED PNEUMONIA

Although CAP is common, agreement on its essential clinical signs and symptoms is surprisingly limited, due in part to heterogeneous patient presentations and in part to interobserver variability. The reader is referred to two excellent reviews on this topic.[28,29]

The diagnosis of CAP is made on clinical grounds, based on a combination of signs and symptoms. Symptoms of pneumonia can include cough, fever, chills, sputum production, dyspnea, and pleuritic pain. Physical findings can include tachypnea, tachycardia, hypoxemia, and consolidation or rales on auscultation. Laboratory data may show leukocytosis or elevated C-reactive protein, and radiographic studies may show evidence of a new infiltrate.[21,30,31]

Although CAP is common, agreement on its essential clinical signs and symptoms is surprisingly limited

Clinical presentation of influenza

Seasonal influenza as a cause of CAP is difficult to distinguish from bacterial causes. The clinical presentation of seasonal influenza most commonly includes fever or subjective feverishness, cough, myalgia, and weakness.[32] In a recent multivariate analysis, five clinical features were shown to be predictive of pandemic H1N1 influenza pneumonia rather than CABP: age younger than 65 years, absence of confusion, white blood cell count less than 12×10^9/L, temperature higher than 38°C (100.4°F), and bilateral opacities on radiography.[32,33]

Complicated influenza infection can be either primary viral pneumonia or bacterial superinfection.

During the 1918 influenza pandemic, which predated the ability to isolate viruses, two clinical syndromes emerged: an ARDS associated with the rapid onset of cyanosis, delirium, and frothy blood-tinged sputum; and an acute bronchopneumonia characterized by necrosis, hemorrhage, edema, and vasculitis.[34,35] The first syndrome has subsequently been shown to be associated with primary viral pneumonia, while the second is caused by bacterial superinfection. Modern reexamination of 1918 data has shown that bacterial superinfection was likely the reason for the distinctly fulminant presentation of that pandemic.[36,37]

The 2009 H1N1 influenza pandemic caused relatively mild disease in most patients. However, those with severe pneumonia more commonly developed ARDS from primary influenza pneumonia than from bacterial superinfection.[17]

A third influenza-associated infection is secondary bacterial pneumonia, which follows influenza infection and mimics the presentation of CABP. A typical patient presents with a recent history of influenza-like illness, followed 4 to 14 days later by a recurrence of fever, dyspnea, productive cough, and consolidation on chest radiographs.[38] Leukocytosis with an increased number of immature neutrophil forms, prolonged duration of fever, and elevated erythrocyte sedimentation rate are more likely in patients with secondary bacterial pneumonia.[39] Isolates from sputum samples commonly include *S pneumoniae*, *S aureus*, *H influenzae*, and other gram-negative rods.[40]

In recent flu seasons, methicillin-resistant *S aureus* (MRSA) has emerged as a cause of severe secondary pneumonia. Most of these isolates carry genes for the toxin Panton-Valentine leukocidin; the associated mortality rate is as high as 33%.[41,42] Although community-acquired MRSA pneumonia has only been reported in case series, distinct clinical features that have been described include severe pneumonia with high fever, hypotension, shock, respiratory failure, leukopenia, and multilobar and cavitary infiltrates.[43]

WHEN TO SUSPECT INFLUENZA

The triad of fever, cough, and abrupt onset are the best predictors of influenza, but no single combination of signs and symptoms predict in-

fluenza infection with 100% certainty. Therefore, an understanding of local epidemiologic data regarding circulating influenza is essential to maintain a high index of suspicion.[44]

It is appropriate to suspect influenza in:

- Anyone who is epidemiologically linked to a known outbreak of influenza
- Children, adults, and health care workers who have fever and abrupt onset of respiratory symptoms
- Patients with fever plus exacerbation of underlying pulmonary disease
- Severely ill patients with fever or hypothermia, especially during influenza season.[45]

DIAGNOSTIC TESTING

Once the diagnosis of pulmonary infection is suggested by clinical features, the initial evaluation should include measurement of vital signs, physical examination, and radiographic imaging of the chest. Additional diagnostic measures to consider include viral testing, blood culture, sputum culture, urinary antigen testing for *Legionella* and for *S pneumoniae*, fungal culture, and mycobacterial smear and culture.

Chest radiography (with posterior-anterior and lateral films) is the study that usually demonstrates the presence of a pulmonary infiltrate. If initial chest radiographs do not show an infiltrate, imaging can be repeated after treatment is started if the patient's clinical presentation still suggests pneumonia. Chest radiographs are of limited value in predicting the pathogen, but they help to determine the extent of pneumonia and to detect parapneumonic effusion.[46]

A caveat: anterior-posterior, posterior-anterior, and lateral views can miss more than 10% of effusions large enough to warrant thoracentesis, especially when there is lower-lobe consolidation.[47]

Blood cultures are recommended for patients admitted to the intensive care unit and for those with cavitary infiltrates, leukopenia, alcohol abuse, severe liver disease, asplenia, positive pneumococcal urinary antigen testing, or a pleural effusion.[21] However, blood cultures are positive in only 3% to 14% of hospitalized patients with CABP, and the impact of a positive blood culture on management decisions in CABP appears to be quite small.[48–50]

For the highest yield, blood culture results should be obtained before antibiotics are given. Not only is this good practice, but obtaining blood culture results before starting antibiotics is one of the quality measures evaluated by the Center for Medicare and Medicaid Services.[51]

Sputum culture is considered optional for outpatients and patients with less-severe pneumonia.[21] While it can provide a rapid diagnosis in certain cases, a good-quality sputum sample is obtained in only 39% to 54% of patients with CABP, yields a predominant morphotype in only 45% of cases, and provides a useful microbiologic diagnosis in only 14.4%.[52,53] Fungal and mycobacterial cultures are only indicated in certain situations such as cavitary infiltrates or immunosuppression.

Urinary antigen testing for *Legionella* and *S pneumoniae* should be done in patients with more severe illness and in those for whom outpatient therapy has failed.[21] *S pneumoniae* testing has been shown to allow early diagnosis of pneumococcal pneumonia in 26% more patients than with Gram staining, but it fails to identify 22% of the rapid diagnoses initially identified by Gram staining.[54] Thus, a sequential approach is reasonable, with urinary antigen testing for patients at high risk without useful results from sputum Gram staining. Also, recent data suggest that the pneumococcal urinary antigen test may allow optimization of antimicrobial therapy with good clinical outcomes.[55]

In recent flu seasons, MRSA has emerged as a cause of severe secondary pneumonia

Endotracheal tests. If the patient is intubated, collection of endotracheal aspirates, bronchoscopy, or nonbronchoscopic bronchial lavage (sometimes called "mini-BAL") should be performed.

Thoracentesis and pleural fluid cultures should be done if a pleural effusion is found. Empyema, large or loculated effusions, and parapneumonic effusions with a pH lower than 7.20, glucose levels less than 3.4 mmol/L (60 mg/dL), or positive results on microbial staining or culture should be drained by chest tube or surgically.[56]

Testing for influenza should be done if it will change the clinical management, such as the choice of antibiotic or infection control practices. Specimens should be obtained with either a nasopharyngeal swab or aspirate and tested with reverse transcriptase polymerase

TABLE 1

Does the patient need to be hospitalized? The Pneumonia Severity Index

CHARACTERISTIC	POINTS
Age > 50 years (men)	Patient's age
Age > 50 years (women)	Patient's age – 10
Neoplastic disease	30
Congestive heart failure	10
Cerebrovascular disease	10
Liver disease	20
Renal disease	10
Altered mental status	20
Pulse ≥ 125/min	10
Respiratory rate ≥ 30/min	20
Temperature < 35°C or ≥ 40°C	15
Systolic blood pressure < 90 mm Hg	20
(If none of the above is present, assign to risk class 1. If one or more are present, calculate the score for classes 2–5.)	
Arterial pH < 7.35	30
Blood urea nitrogen ≥ 30 mg/dL (11 mmol/L)	20
Sodium < 130 mmol/L	20
Glucose ≥ 250 mg/dL (14 mmol/L)	10
Hematocrit < 30%	10
Partial pressure of arterial oxygen < 60 mm Hg	10
Pleural effusion	10
Total	____

Risk classes

TOTAL POINTS	CLASS	MORTALITY RISK
0	1	Low (0.1%–0.4%)
1–70	2	Low (0.6%–0.7%)
71–90	3	Low (0.9%–2.8%)
91–130	4	Intermediate (8.2%–9.3%)
> 130	5	High (27%–31%)

Patients in low-risk classes 1–3 can be considered for outpatient care, while those in classes 4 and 5 likely need hospitalization.

BASED ON FINE, MJ, AUBLE TE, YEALY DM, ET AL. A PREDICTION RULE TO IDENTIFY LOW-RISK PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA. N ENGL J MED 1997; 336:243–250.

chain reaction, immunofluorescent staining, or rapid antigen detection, depending on local availability.[45]

Inflammatory biomarkers such as C-reactive protein and procalcitonin have been receiving interest as ways to predict the etiology and prognosis of CAP and to guide therapy. Several studies have shown that C-reactive protein can help distinguish between CAP and bronchitis, with higher values suggesting more severe pneumonia and pneumonia caused by *S pneumoniae* or *L pneumophila*.[57] Procalcitonin may help discriminate between severe lower respiratory tract infections of bacterial and 2009 H1N1 origin, although less effectively than C-reactive protein. Low procalcitonin values, particularly when combined with low C-reactive protein levels, suggest that bacterial infection is unlikely.[58]

RISK STRATIFICATION AND SITE-OF-CARE DECISIONS

Following a presumptive diagnosis of CAP, it is important to decide not only what treatment the patient will receive but whether he or she should be hospitalized. If the patient is to be admitted to the hospital, the clinician must also decide if his or her condition warrants intensive care.

Severity-of-illness scores

Several severity-of-illness scores and prognostic models have been validated for use in deciding on inpatient vs outpatient treatment and to aid in the decision of whether a patient with pneumonia should be admitted to an intensive care unit. The most extensively studied and widely used scoring systems are the Pneumonia Severity Index (PSI) (TABLE 1)[59] and the CURB-65 (FIGURE 1).[60]

The PSI is the more complicated of the two, as it is based on 19 variables. Online calculators are available for the PSI (http://pda.ahrq.gov/clinic/psi/psicalc.asp) and the CURB-65 (http://www.mdcalc.com/curb-65-severity-score-community-acquired-pneumonia).

A recent meta-analysis compared the performance characteristics of the PSI and CURB-65 scores for predicting mortality in CAP and found no significant differences in

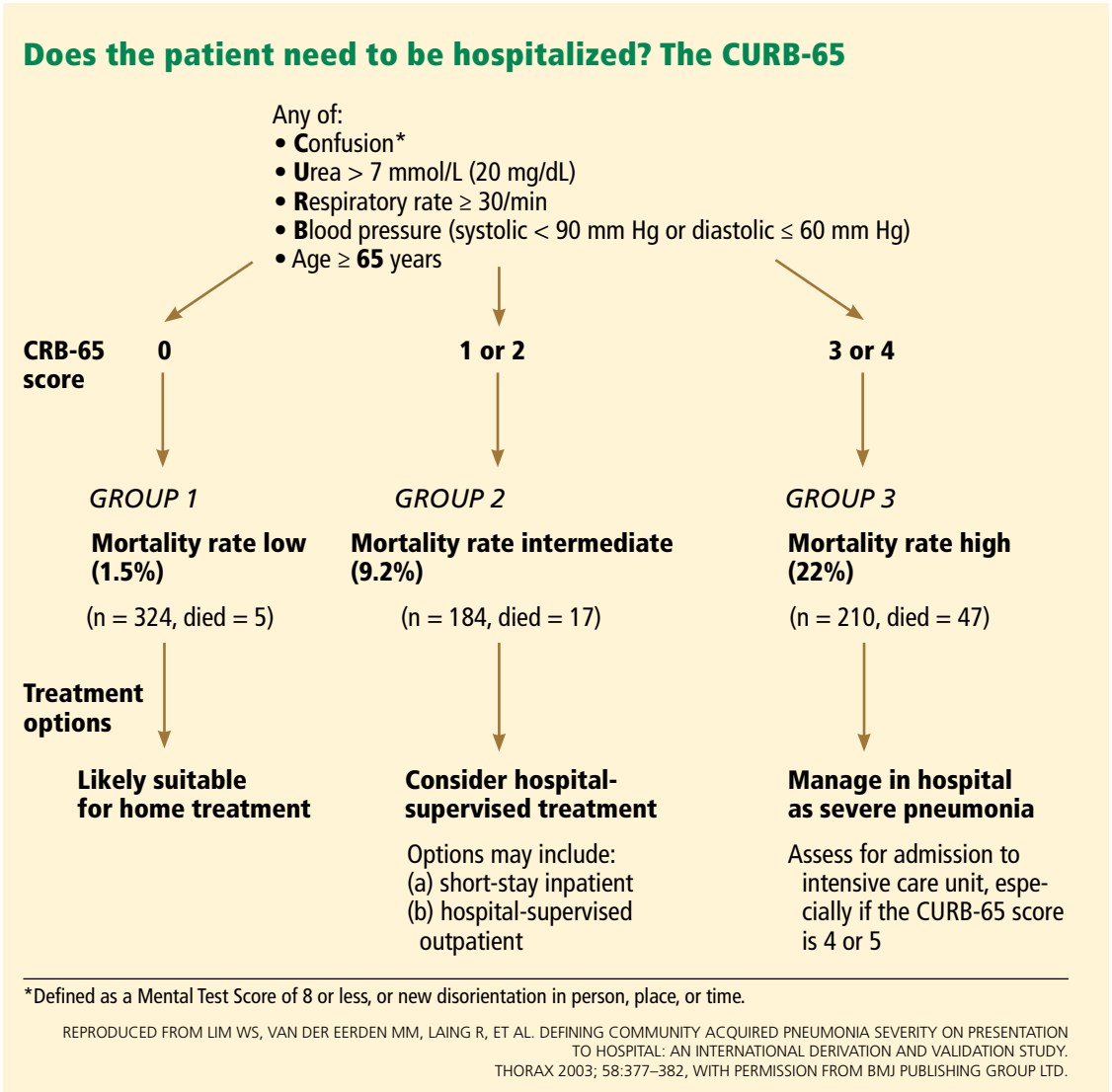

FIGURE 1

overall test performance.[61]

Another meta-analysis found that the PSI was more sensitive than the CURB-65 and had a low false-negative rate, and so was better at showing which patients do not need to be hospitalized. Conversely, the CURB-65 was more specific and had a higher positive predictive value, and thus was more likely to correctly classify high-risk patients.[62]

Other scoring systems that aid in deciding about hospital admission and level of care include the CRB-65[63] (which can be used instead of the CURB-65 if laboratory values are not available), SMART-COP,[64] and SCAP.[65]

Guidelines on when to admit to the intensive care unit

Guidelines from the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) also provide guidance on when intensive care admission is advised,[21] and their criteria were recently validated.[66] The guidelines advocate direct admission to the intensive care unit for patients requiring vasopressors or mechanical ventilation, and intensive care unit or high-level monitoring for patients with three of the following criteria for severe CAP[21]:

- Respiratory rate ≥ 30
- Pao_2/Fio_2 ratio ≤ 250

Low procalcitonin, particularly when combined with low C-reactive protein, suggests that bacterial infection is unlikely

- Multilobar infiltrates
- Confusion or disorientation
- Uremia (blood urea nitrogen ≥ 20 mg/dL)
- Leukopenia (white blood cell count < 4.0 × 10^9/L)
- Thrombocytopenia (platelet count < 100 × 10^9/L)
- Hypothermia (core temperature < 36.0°C [96.8°F])
- Hypotension requiring aggressive fluid resuscitation.

None of these scoring systems or criteria is meant to replace clinical judgment. A recent study has suggested that an oxygen saturation of less than 92% is an appropriate threshold for hospital admission, in view of higher rates of adverse events in outpatients with saturations below this value.[67]

TREATMENT

Multiple studies have shown that treatment of CAP in accordance with guidelines has led to improved clinical outcomes.[21,68–70]

How fast must antibiotics be started?

None of these scoring systems or criteria is meant to replace clinical judgment

Based on studies that showed a lower mortality rate when antibiotics were started sooner, Medicare and Medicaid adopted a quality measure calling for starting antibiotics within 4 hours in patients being admitted to the hospital.[50,71] However, several subsequent studies showed that the diagnosis of pneumonia is often incorrect and that rapid administration of antibiotics could lead to misdiagnosis, overuse of antibiotics, and a higher risk of *Clostridium difficile* infection.[72,73]

The current IDSA/ATS guidelines[21] recommend that the first antibiotic dose be given while the patient is still in the emergency department, but do not give a specific time within which it should be given. Medicare and Medicaid later updated their quality measure to antibiotic administration within 6 hours.

Which antibiotics should be used?

The selection of antimicrobial agent depends upon the patient's severity of illness and comorbid conditions.

Although most studies of combination antibiotic therapy have been retrospective and observational, they suggest that a macrolide (ie, one of the "mycins") added to a beta-lactam antibiotic is beneficial, possibly by covering atypical organisms or via anti-inflammatory action.[74–76] The choice of one antibiotic over another appears to be less important, and a recent Cochrane review concluded that there was no significant difference in efficacy among five antibiotic pairs studied.[77]

Empiric outpatient treatment of a previously healthy patient with CAP and no risk factors for drug-resistant *S pneumoniae* should include either a macrolide (azithromycin [Zithromax], clarithromycin [Biaxin], or erythromycin) or doxycycline. If the patient has a chronic comorbid condition such as heart, lung, liver, or renal disease, diabetes mellitus, alcoholism, malignancy, asplenia, or immunosuppression or has received antimicrobials within the preceding 3 months, then treatment should include either a respiratory fluoroquinolone (moxifloxacin [Avelox] or levofloxacin [Levaquin]) or a beta-lactam plus a macrolide.[21]

Overall, published data suggest that the survival rate is about the same with fluoroquinolone monotherapy as with beta-lactam plus macrolide combination therapy, and better than with beta-lactam monotherapy.[78]

Selection of antibiotics for inpatient treatment of CAP is influenced by severity of illness. Inpatients who do not require intensive care should be treated with either a respiratory fluoroquinolone or combination therapy with a beta-lactam (cefotaxime [Claforan], ceftriaxone [Rocephin], ampicillin, or ertapenem [Invanz]) plus a macrolide or doxycycline.[21,76,79]

If a specific microbiologic diagnosis is made, then treatment can be narrowed. However in certain cases, such as invasive pneumococcal infection, combination therapy may still be superior.[80,81] For patients who need intensive care, treatment should always include a beta-lactam plus either azithromycin or a respiratory fluoroquinolone.[21] In certain situations, additional antibiotics may be added as well, such as agents to treat *Pseudomonas*, community-acquired MRSA, or both.

Switching to oral therapy; short-course therapy

In the interest of avoiding unnecessary antibiotics, numerous studies have addressed the is-

sue of an "early switch" to oral antibiotics and "short-course" therapy for CAP. In general, once clinically stable, patients with CAP, including bacteremic *S pneumoniae* pneumonia, can be safely switched to oral antibiotics.[82]

The issue of short-course therapy is more complicated, and the appropriate length of therapy for CAP is not well established. However, 5 days of levofloxacin 750 mg was shown to be as successful as 7 to 10 days of levofloxacin 500 mg.[83] In another study, in patients who improved after 3 days of intravenous therapy for CAP, there was no difference in clinical outcome between those who were changed to oral therapy for 5 more days and those who received an oral placebo.[84]

Most patients who achieve clinical stability in the first week do not need prolonged antibiotic therapy. However, certain conditions, such as *S aureus* bacteremic pneumonia, complicated pneumonia, and pneumonia due to unusual organisms, may require prolonged treatment.

Other therapies

Additional therapies studied in patients with pneumonia include early mobilization, adjunctive corticosteroids, and statin drugs.

Early mobilization was shown in one study to decrease hospital length of stay without increasing adverse effects.[85]

Corticosteroids are not supported as a standard of care for patients with severe CAP according to current available studies.[86,87] Furthermore, a randomized, controlled trial showed that prednisolone daily for a week did not improve outcomes in hospitalized patients with CAP, and it was associated with increased late failure.[88]

Statin trials under way. Several observational studies have suggested that statins might be beneficial in managing sepsis through their effects on endothelial cell function, antioxidant effects, anti-inflammatory effects, and immunomodulatory effects.[89] However, a recent large prospective multicenter cohort study of hospitalized patients with CAP did not find evidence of a protective effect of statins on clinically meaningful outcomes in CAP or significant differences in circulating biomarkers.[90] Several randomized trials of statin therapy in patients with both ventilator-associated pneumonia and CAP are under way.

INFLUENZA TREATMENT: MOST EFFECTIVE WITHIN 48 HOURS

Treatment with antiviral drugs is most effective if started within 48 hours after symptom onset, although some patients with confirmed influenza who are either not improving or who are critically ill may still benefit from treatment started later.

Treatment should be considered in patients with laboratory-confirmed or suspected influenza who are at risk of developing complicated influenza and in otherwise healthy patients who wish to reduce the duration of illness or who have close contact with patients who are at high risk of complications.

Antiviral medications are oseltamivir (Tamiflu), zanamivir (Relenza), and the adamantines amantadine (Symmetrel) and rimantadine (Flumadine).

Due to evolving viral resistance patterns, the choice of antiviral drug depends on the strain. Seasonal H1N1 is best treated with zanamivir or an adamantine, while pandemic 2009 H1N1 and H3N2 are best treated with zanamivir or oseltamivir. When strain typing is not available, empiric therapy should be with either zanamivir monotherapy or a combination of oseltamivir plus rimantadine. Influenza B viruses are resistant to adamantines and should be treated only with either zanamivir or oseltamivir.[45]

Chest films can miss > 10% of effusions large enough to warrant thoracentesis, especially when there is lower lobe consolidation

FOLLOW-UP AND PREVENTION

Patients with CAP can generally be expected to improve within 3 to 7 days.[91] However, it may be several weeks before they return to baseline.[92]

Follow-up plans may be guided by the time to clinical stability. For patients who do not achieve clinical stability until more than 72 hours after admission, more aggressive follow-up on discharge is indicated, since they are more likely to experience early readmission and death.[93]

Pneumococcal vaccination. Because *S pneumoniae* remains the most common cause of CAP, efforts should be made to vaccinate patients appropriately. The Advisory Committee on Immunization Practices (ACIP)

and the US Centers for Disease Control and Prevention recommend that the pneumococcal polysaccharide vaccine (Pneumovax 23; PPSV23) be given to those over age 65. Those who were vaccinated before age 65 should receive another dose at age 65 or later if at least 5 years have passed since their previous dose. Those who receive it at or after age 65 should receive only a single dose. A second dose is recommended 5 years after the first dose for people age 19 to 64 years with functional or anatomic asplenia and for those who are immunocompromised.

Influenza vaccination for all. Of note, the ACIP updated its guidelines on influenza vaccination beginning with the 2010–2011 influenza season. It no longer advocates a risk-stratified approach. Instead, it recommends universal influenza vaccination for everybody more than 6 months old.[94]

Smoking cessation should be addressed. Smoking cessation is a Medicare and Medicaid quality measure and should be encouraged after an episode of CAP because quitting smoking reduces the risk of pneumococcal disease by approximately 14% each year thereafter.[95]

REFERENCES

1. **Mortensen EM, Kapoor WN, Chang CC, Fine MJ**. Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. Clin Infect Dis 2003; 37:1617-1624.
2. **File TM Jr, Marrie TJ**. Burden of community-acquired pneumonia in North American adults. Postgrad Med 2010; 122:130–141.
3. **Marston BJ, Plouffe JF, File TM Jr, et al**. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance study in Ohio. The Community-Based Pneumonia Incidence Study Group. Arch Intern Med 1997; 157:1709–1718.
4. **Fine MJ, Smith MA, Carson CA, et al**. Prognosis and outcomes of patients with community-acquired pneumonia. JAMA 1996; 275:134–141.
5. **Ruhnke GW, Coca-Perraillon M, Kitch BT, Cutler DM**. Trends in mortality and medical spending in patients hospitalized for community-acquired pneumonia: 1993–2005. Med Care 2010; 48:1111–1116.
6. **Jackson ML, Neuzil KM, Thompson WW, et al**. The burden of community-acquired pneumonia in seniors: results of a population-based study. Clin Infect Dis 2004; 39:1642–1650.
7. **Koivula I, Sten M, Mäkelä PH**. Risk factors for pneumonia in the elderly. Am J Med 1994; 96:313–320.
8. **Ruhnke GW, Coca-Perraillon M, Kitch BT, Cutler DM**. Marked reduction in 30-day mortality among elderly patients with community-acquired pneumonia. Am J Med 2011; 124:171–178.
9. **Farr BM, Bartlett CL, Wadsworth J, Miller DL**. Risk factors for community-acquired pneumonia diagnosed upon hospital admission. British Thoracic Society Pneumonia Study Group. Respir Med 2000; 94:954–963.
10. **Graves CR**. Pneumonia in pregnancy. Clin Obstet Gynecol 2010; 53:329–336.
11. **Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS**. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. CMAJ 2011; 183:310–319.
12. **Voiriot G, Dury S, Parrot A, Mayaud C, Fartoukh M**. Nonsteroidal antiinflammatory drugs may affect the presentation and course of community-acquired pneumonia. Chest 2011; 139:387–394.
13. **Thompson WW, Shay DK, Weintraub E, et al**. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003; 289:179–186.
14. **Thompson WW, Shay DK, Weintraub E, et al**. Influenza-associated hospitalizations in the United States. JAMA 2004; 292:1333–1340.
15. **Glezen WP, Decker M, Perrotta DM**. Survey of underlying conditions of persons hospitalized with acute respiratory disease during influenza epidemics in Houston, 1978-1981. Am Rev Respir Dis 1987; 136:550–555.
16. **Izurieta HS, Thompson WW, Kramarz P, et al**. Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med 2000; 342:232–239.
17. **Rothberg MB, Haessler SD**. Complications of seasonal and pandemic influenza. Crit Care Med 2010; 38(suppl 4):e91–e97.
18. **Apisarnthanarak A, Mundy LM**. Etiology of community-acquired pneumonia. Clin Chest Med 2005; 26:47–55.
19. **de Roux A, Marcos MA, Garcia E, et al**. Viral community-acquired pneumonia in nonimmunocompromised adults. Chest 2004; 125:1343–1351.
20. **Hamelin ME, Côté S, Laforge J, et al**. Human metapneumovirus infection in adults with community-acquired pneumonia and exacerbation of chronic obstructive pulmonary disease. Clin Infect Dis 2005; 41:498–502.
21. **Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society**. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44(suppl 2):S27–S72.
22. **Kolling UK, Hansen F, Braun J, Rink L, Katus HA, Dalhoff K**. Leucocyte response and anti-inflammatory cytokines in community acquired pneumonia. Thorax 2001; 56:121–125.
23. **Wunderink RG, Waterer GW**. Community-acquired pneumonia: pathophysiology and host factors with focus on possible new approaches to management of lower respiratory tract infections. Infect Dis Clin North Am 2004; 18:743–759.
24. **Hilleman MR**. Realities and enigmas of human viral influenza: pathogenesis, epidemiology and control. Vaccine 2002; 20:3068–3087.
25. **Bender BS, Small PA Jr**. Influenza: pathogenesis and host defense. Semin Respir Infect 1992; 7:38–45.
26. **Scheiblauer H, Reinacher M, Tashiro M, Rott R**. Interactions between bacteria and influenza A virus in the development of influenza pneumonia. J Infect Dis 1992; 166:783–791.
27. **McCullers JA**. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev 2006; 19:571–582.
28. **Metlay JP, Kapoor WN, Fine MJ**. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. JAMA 1997; 278:1440–1445.
29. **Benbassat J, Baumal R**. Narrative review: should teaching of the respiratory physical examination be restricted only to signs with proven reliability and validity? J Gen Intern Med 2010; 25:865–872.
30. **Kolsuz M, Erginel S, Alatas O, et al**. Acute phase reactants and cytokine levels in unilateral community-acquired pneumonia. Respiration 2003; 70:615–622.
31. **Alves DW, Kennedy MT**. Community-acquired pneumonia in casualty: etiology, clinical features, diagnosis, and management (or a look at the "new" in pneumonia since 2002). Curr Opin Pulm Med 2004; 10:166–170.
32. **Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J**. Clinical signs and symptoms predicting influenza infection. Arch Intern Med 2000; 160:3243–3247.
33. **Bewick T, Myles P, Greenwood S, et al; Influenza Clinical Information Network**. Clinical and laboratory features distinguishing pandemic H1N1 influenza-related pneumonia from interpandemic community-acquired pneumonia in adults. Thorax 2011; 66:247–252.

34. **Morens DM, Fauci AS**. The 1918 influenza pandemic: insights for the 21st century. J Infect Dis 2007; 195:1018–1028.
35. **Starr I**. Influenza in 1918: recollections of the epidemic in Philadelphia. 1976. Ann Intern Med 2006; 145:138–140.
36. **Morens DM, Taubenberger JK, Fauci AS**. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis 2008; 198:962–970.
37. **Brundage JF, Shanks GD**. Deaths from bacterial pneumonia during 1918-19 influenza pandemic. Emerg Infect Dis 2008; 14:1193–1199.
38. **Treanor J**. Influenza virus. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. 6th ed. Philadelphia, PA: Elsevier/Churchill Livingstone; 2005:2060–2085.
39. **Jarstrand C, Tunevall G**. The influence of bacterial superinfection on the clinical course of influenza. Studies from the influenza epidemics in Stockholm during the winters 1969-70 and 1971-72. Scand J Infect Dis 1975; 7:243–247.
40. **Schwarzmann SW, Adler JL, Sullivan RJ Jr, Marine WM**. Bacterial pneumonia during the Hong Kong influenza epidemic of 1968-1969. Arch Intern Med 1971; 127:1037–1041.
41. **Hageman JC, Uyeki TM, Francis JS, et al**. Severe community-acquired pneumonia due to Staphylococcus aureus, 2003-04 influenza season. Emerg Infect Dis 2006; 12:894–899.
42. **Centers for Disease Control and Prevention (CDC)**. Severe methicillin-resistant Staphylococcus aureus community-acquired pneumonia associated with influenza—Louisiana and Georgia, December 2006-January 2007. MMWR Morb Mortal Wkly Rep 2007; 56:325–329.
43. **Hidron AI, Low CE, Honig EG, Blumberg HM**. Emergence of community-acquired methicillin-resistant Staphylococcus aureus strain USA300 as a cause of necrotising community-onset pneumonia. Lancet Infect Dis 2009; 9:384–392.
44. **Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP**. Does this patient have influenza? JAMA 2005; 293:987–997.
45. **Harper SA, Bradley JS, Englund JA, et al; Expert Panel of the Infectious Diseases Society of America**. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:1003–1032.
46. **Boersma WG, Daniels JM, Löwenberg A, Boeve WJ, van de Jagt EJ**. Reliability of radiographic findings and the relation to etiologic agents in community-acquired pneumonia. Respir Med 2006; 100:926–932.
47. **Brixey AG, Luo Y, Skouras V, Awdankiewicz A, Light RW**. The efficacy of chest radiographs in detecting parapneumonic effusions. Respirology 2011; 16:1000–1004.
48. **Campbell SG, Marrie TJ, Anstey R, Dickinson G, Ackroyd-Stolarz S**. The contribution of blood cultures to the clinical management of adult patients admitted to the hospital with community-acquired pneumonia: a prospective observational study. Chest 2003; 123:1142–1150.
49. **Waterer GW, Wunderink RG**. The influence of the severity of community-acquired pneumonia on the usefulness of blood cultures. Respir Med 2001; 95:78–82.
50. **Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG**. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med 2004; 164:637–644.
51. **Information & Quality Healthcare**. http://www.IQH.org/attachments/219_CoreMHelpBookletpg4_11_3.pdf. Accessed November 14, 2011.
52. **Rosón B, Carratalà J, Verdaguer R, Dorca J, Manresa F, Gudiol F**. Prospective study of the usefulness of sputum Gram stain in the initial approach to community-acquired pneumonia requiring hospitalization. Clin Infect Dis 2000; 31:869–874.
53. **García-Vázquez E, Marcos MA, Mensa J, et al**. Assessment of the usefulness of sputum culture for diagnosis of community-acquired pneumonia using the PORT predictive scoring system. Arch Intern Med 2004; 164:1807–1811.
54. **Rosón B, Fernández-Sabé N, Carratalà J, et al**. Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. Clin Infect Dis 2004; 38:222–226.
55. **Sordé R, Falcó V, Lowak M, et al**. Current and potential usefulness of pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia to guide antimicrobial therapy. Arch Intern Med 2011; 171:166–172.
56. **Koegelenberg CFN, Diacon AH, Bolliger CT**. Parapneumonic pleural effusion and empyema. Respiration 2008; 75:241–250.
57. **Almirall J, Bolíbar I, Toran P, et al; Community-Acquired Pneumonia Maresme Study Group**. Contribution of C-reactive protein to the diagnosis and assessment of severity of community-acquired pneumonia. Chest 2004; 125:1335–1342.
58. **Ingram PR, Inglis T, Moxon D, Speers D**. Procalcitonin and C-reactive protein in severe 2009 H1N1 influenza infection. Intensive Care Med 2010; 36:528–532.
59. **Fine MJ, Auble TE, Yealy DM, et al**. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 336:243–250.
60. **Lim WS, van der Eerden MM, Laing R, et al**. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58:377–382.
61. **Chalmers JD, Singanayagam A, Akram AR, et al**. Severity assessment tools for predicting mortality in hospitalised patients with community-acquired pneumonia. Systematic review and meta-analysis. Thorax 2010; 65:878–883.
62. **Loke YK, Kwok CS, Niruban A, Myint PK**. Value of severity scales in predicting mortality from community-acquired pneumonia: systematic review and meta-analysis. Thorax 2010; 65:884–890.
63. **Capelastegui A, España PP, Quintana JM, et al**. Validation of a predictive rule for the management of community-acquired pneumonia. Eur Respir J 2006; 27:151–157.
64. **Charles PG, Wolfe R, Whitby M, et al; Australian Community-Acquired Pneumonia Study Collaboration**. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. Clin Infect Dis 2008; 47:375–384.
65. **España PP, Capelastegui A, Gorordo I, et al**. Development and validation of a clinical prediction rule for severe community-acquired pneumonia. Am J Respir Crit Care Med 2006; 174:1249–1256.
66. **Chalmers JD, Taylor JK, Mandal P, et al**. Validation of the Infectious Diseases Society of America/American Thoracic Society minor criteria for intensive care unit admission in community-acquired pneumonia patients without major criteria or contraindications to intensive care unit care. Clin Infect Dis 2011; 53:503–511.
67. **Majumdar SR, Eurich DT, Gamble JM, Senthilselvan A, Marrie TJ**. Oxygen saturations less than 92% are associated with major adverse events in outpatients with pneumonia: a population-based cohort study. Clin Infect Dis 2011; 52:325–331.
68. **Nathwani D, Rubinstein E, Barlow G, Davey P**. Do guidelines for community-acquired pneumonia improve the cost-effectiveness of hospital care? Clin Infect Dis 2001; 32:728–741.
69. **Dean NC, Silver MP, Bateman KA, James B, Hadlock CJ, Hale D**. Decreased mortality after implementation of a treatment guideline for community-acquired pneumonia. Am J Med 2001; 110:451–457.
70. **Capelastegui A, España PP, Quintana JM, et al**. Improvement of process-of-care and outcomes after implementing a guideline for the management of community-acquired pneumonia: a controlled before-and-after design study. Clin Infect Dis 2004; 39:955–963.
71. **Silber SH, Garrett C, Singh R, et al**. Early administration of antibiotics does not shorten time to clinical stability in patients with moderate-to-severe community-acquired pneumonia. Chest 2003; 124:1798–1804.
72. **Welker JA, Huston M, McCue JD**. Antibiotic timing and errors in diagnosing pneumonia. Arch Intern Med 2008; 168:351–356.
73. **Polgreen PM, Chen YY, Cavanaugh JE, et al**. An outbreak of severe Clostridium difficile-associated disease possibly related to inappropriate antimicrobial therapy for community-acquired pneumonia. Infect Control Hosp Epidemiol 2007; 28:212–214.
74. **Waterer GW, Somes GW, Wunderink RG**. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001; 161:1837–1842.
75. **Lodise TP, Kwa A, Cosler L, Gupta R, Smith RP**. Comparison of beta-lactam and macrolide combination therapy versus fluoroquinolone monotherapy in hospitalized Veterans Affairs patients with community-acquired pneumonia. Antimicrob Agents Chemother 2007; 51:3977–3982.

76. **Waterer GW, Rello J, Wunderink RG**. Management of community-acquired pneumonia in adults. Am J Respir Crit Care Med 2011; 183:157–164.
77. **Bjerre LM, Verheij TJ, Kochen MM**. Antibiotics for community acquired pneumonia in adult outpatients. Cochrane Database Syst Rev 2009; (4):CD002109.
78. **Frei CR, Labreche MJ, Attridge RT**. Fluoroquinolones in community-acquired pneumonia: guide to selection and appropriate use. Drugs 2011; 71:757–770.
79. **Weiss K, Tillotson GS**. The controversy of combination vs monotherapy in the treatment of hospitalized community-acquired pneumonia. Chest 2005; 128:940–946.
80. **Martínez JA, Horcajada JP, Almela M, et al**. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2003; 36:389–395.
81. **Waterer GW, Somes GW, Wunderink RG**. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001; 161:1837–1842.
82. **Ramirez JA, Bordon J**. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-acquired Streptococcus pneumoniae pneumonia. Arch Intern Med 2001; 161:848–850.
83. **Dunbar LM, Wunderink RG, Habib MP, et al**. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clin Infect Dis 2003; 37:752–760.
84. **el Moussaoui R, de Borgie CA, van den Broek P, et al**. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. BMJ 2006; 332:1355.
85. **Mundy LM, Leet TL, Darst K, Schnitzler MA, Dunagan WC**. Early mobilization of patients hospitalized with community-acquired pneumonia. Chest 2003; 124:883–889.
86. **Salluh JI, Póvoa P, Soares M, Castro-Faria-Neto HC, Bozza FA, Bozza PT**. The role of corticosteroids in severe community-acquired pneumonia: a systematic review. Crit Care 2008; 12:R76.
87. **Mikami K, Suzuki M, Kitagawa H, et al**. Efficacy of corticosteroids in the treatment of community-acquired pneumonia requiring hospitalization. Lung 2007; 185:249–255.
88. **Snijders D, Daniels JM, de Graaff CS, van der Werf TS, Boersma WG**. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. Am J Respir Crit Care Med 2010; 181:975–982.
89. **Chopra V, Flanders SA**. Does statin use improve pneumonia outcomes? Chest 2009; 136:1381–1388.
90. **Yende S, Milbrandt EB, Kellum JA, et al**. Understanding the potential role of statins in pneumonia and sepsis. Crit Care Med 2011; 39:1871–1878.
91. **Halm EA, Fine MJ, Marrie TJ, et al**. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. JAMA 1998; 279:1452–1457.
92. **Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Feagan BG**. Predictors of symptom resolution in patients with community-acquired pneumonia. Clin Infect Dis 2000; 31:1362–1367.
93. **Aliberti S, Peyrani P, Filardo G, et al**. Association between time to clinical stability and outcomes after discharge in hospitalized patients with community-acquired pneumonia. Chest 2011; 140:482–488.
94. **Fiore AE, Uyeki TM, Broder K, et al; Centers for Disease Control and Prevention (CDC)**. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep 2010; 59:1–62.
95. **Nuorti JP, Butler JC, Farley MM, et al**. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med 2000; 342:681–689.

***ADDRESS**: Sarah Haessler, MD, Division of Infectious Diseases, Baystate Medical Center, Tufts University School of Medicine, 3300 Main Street, Suites 3C&D, Springfield, MA 01199; e-mail Sarah.Haessler@baystatehealth.org.*