Community-Acquired Pneumonia

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Objectives:

1. Define the epidemiology of community-acquired pneumonia (CAP) and risk factors for mortality.
2. Discuss the common etiologic pathogens of CAP.
3. Review current treatment strategies for CAP.
4. Discuss the clinical relevance of atypical pathogens and penicillin-resistant pneumococci.
5. Review the benefits of pneumococcal and influenza vaccine.

Key words: atypical pathogens; influenza; pneumococcus; pneumonia; vaccination

Pneumonia and influenza together are the sixth leading cause of death in the United States and the number-one cause of mortality from infectious diseases. Community-acquired pneumonia (CAP) occurs in approximately 6 million people annually, with 20 to 30% requiring hospital admission.

Epidemiology and Risk Factors for Mortality

In a recent meta-analysis, the overall mortality rate among 33,148 patients reported in 127 studies was 13.7%, ranging from 5.1% in a population that included both hospitalized and ambulatory patients to 13.6% for hospitalized patients. In the elderly, mortality was 17.6%, while among nursing home patients it was 30.8%, and among those admitted to the ICU it was 36.5%. When pneumococcus was responsible, the mortality rate was 12.3%, a rate similar to that seen when no pathogen could be identified (12.8%). Certain pathogens such as *Pseudomonas aeruginosa*, other Gram-negative organisms (such as *Klebsiella pneumoniae*), and *Staphylococcus aureus* had higher associated mortality rates.

A number of prognostic factors for mortality were identified, the most important being underlying neurologic disease, BUN > 20 mg/dL, respiratory rate > 20/min, systolic hypotension, hypothermia, bacteremia, multilobar disease, coexisting malignancy, and underlying congestive heart failure. The presence of a comorbid illness, more than specific bacteriology or patient age, is the major determinant of early and late mortality in CAP patients. In one study, 16% of all hospitalized CAP patients died, but an additional 32% of discharged patients died of all causes in the subsequent 2 years. Patients with CAP are at risk for recurrent infection, indicating the need to vaccinate all pneumonia patients prior to discharge in an effort to avoid this complication, which has a very high mortality rate.

The British Thoracic Society rule uses certain clinical and laboratory features to identify certain high-risk patients who might have been unrecognized otherwise, and should be included in the initial evaluation. It uses only three variables: respiratory rate ≥ 30/min, BUN > 19.6 mg/dL, and diastolic blood pressure ≤ 60 mm Hg. The presence of two of these three variables increases mortality 9- to 21-fold. More recently, patient confusion has been added as a fourth variable, and if two of four variables are present, there is a similar increase in risk of death and need for ICU admission. Other factors that are associated with a poor outcome in CAP include age > 65 years, the presence of comorbid illness, altered mental status, temperature > 38.3°C, extrapulmonary sites of infection, extremes of white blood cell count, multilobar radiographic abnormalities, evidence of sepsis, respiratory failure, the presence of end organ dysfunction secondary to severe infection, delays in the initiation of appropriate antibiotic therapy, prolonged illness prior to therapy, and indistinct clinical features on presentation (*ie*, afebrile, absence of pleuritic chest pain). When multiple factors predicting a complicated course are present, hospitalization is indicated.

The pneumonia PORT study has led to the development of a prediction rule for deciding who should be admitted to the hospital with CAP. This rule divides patients into five groups with different risks of death, and suggests that outpatient care be given for classes I and II, admission for classes IV and V, and individualized decision for class III. The system heavily weights age and comorbid illness, and in one prospective study of its use, it was successful in increasing the number of emergency-room patients sent home. However, in that study, outpatient therapy failed in almost 10% of

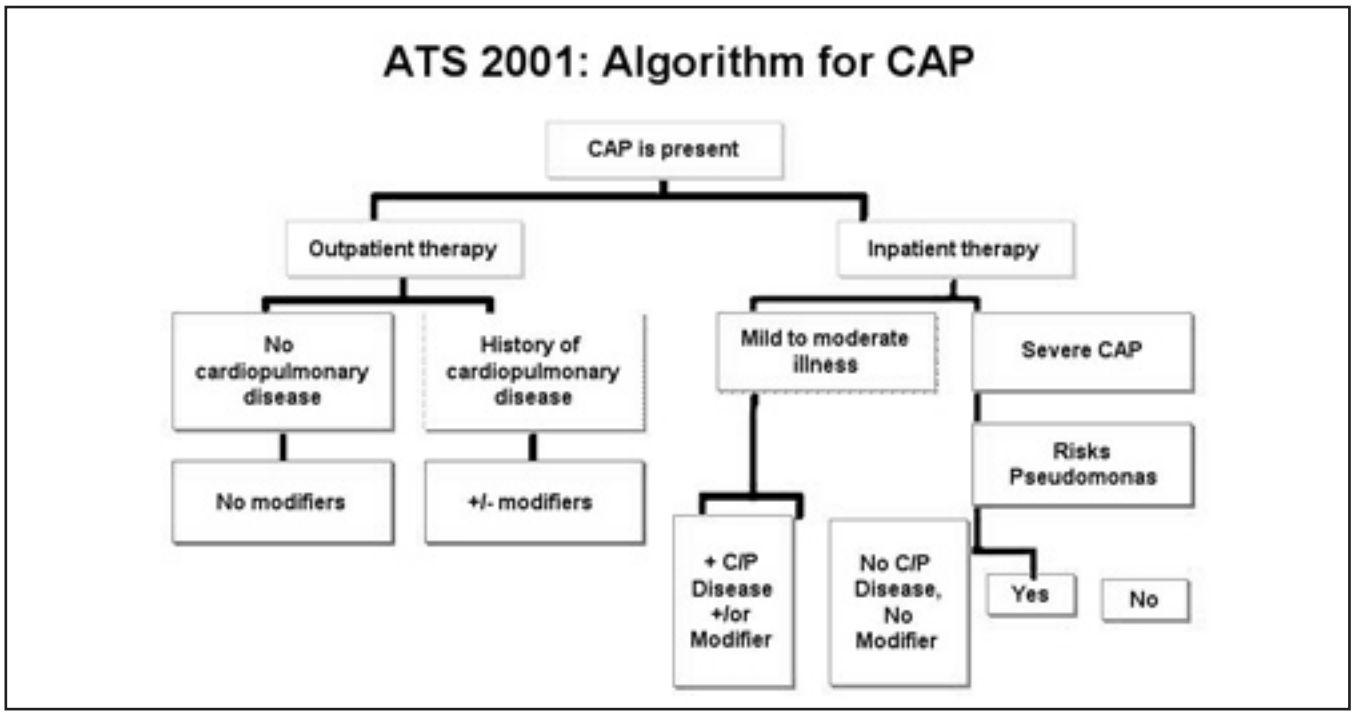

Figure 1. Treatment guidelines.

discharged patients, and patient satisfaction with the discharge decision was lower than when the rule was not used. In a larger study, the rule was successful in increasing the number of low-risk patients who were discharged, compared with situations when the rule was not used, but even at sites that used the rule, 31% of low-risk patients were still admitted, emphasizing the fact that the admission decision remains an "art of medicine" decision that cannot be easily determined by a rule.

Pathogenesis

Most of the pathogens responsible for CAP reach the lung after first colonizing the oropharynx. Since patients with serious comorbidity have an increased risk of Gram-negative colonization of the oropharynx, those same patients appear to have an increased risk of pneumonia due to these types of pathogens. Community respiratory pathogens that can enter via inhalation, without preceding oropharyngeal colonization, include certain viruses, *Mycobacterium tuberculosis*, and Legionella.

One of the serious but infrequent complications of CAP is acute lung injury, presumably due to activation of inflammatory mediators in the lung. Investigators have evaluated the normal host response to pneumonia in order to determine if the inflammatory response remains localized to the lung or if it enters into the systemic circulation, thereby creating the conditions that lead to lung injury and ARDS. In studies of unilateral pneumonia, the infected lung had enhanced production of tumor necrosis factor-α, interleukin (IL)-1β, IL-6, and IL-8 with little effect on the contralateral lung or systemic circulation. IL-8 may be a key mediator because it can recruit neutrophils to sites of infection, and alveolar levels of this cytokine correlate with the number of neutrophils in the alveolar space. The fact that the cytokine response to pneumonia is usually localized may explain why ARDS is an infrequent complication of CAP.

Pathogens

Bacteria, viruses and "atypical pathogens" (*Mycoplasma pneumoniae* and *Chlamydia pneumoniae*) account for most cases of CAP, but in some 50% of patients a microbiologic diagnosis is not established, reflecting the limitations of current diagnostic testing, particularly in those patients who have received prior antibiotic therapy. In one recent study, transthoracic needle aspiration was used in patients without a known diagnosis, and many of these patients were shown to have pneumococcal infection. While this organism can account for many undiagnosed patients, it is also possible that not all pathogens causing CAP have been identified and studied, and new pathogens are commonly being described. The distribution of individual pathogens

has also varied in studies, depending on the location of the study and the types of patients evaluated. For example, in a study of 385 patients at an inner city US hospital, 205 of whom were HIV-negative, pneumococcus was found in 15%, *Haemophilus influenzae* in 7.3%, and atypical pathogens in 8%; in 37% no agent was identified. Most of these patients were older, 65% had a smoking history, and 30% were classified as alcoholic. This distribution of etiologic agents contrasts with the results of a study done in Israel, in which 346 patients were evaluated and a diagnosis was established in 81%. Pneumococcus was found in 43%, *M pneumoniae* in 29%, *C pneumoniae* in 18%, Legionella in 16%, and viruses in 10%. Interestingly, in 38% of the patients, multiple organisms were present simultaneously. In a recent US study, 2,776 patients were studied and a possible etiologic diagnosis was made in 44.3%. In this group, *M pneumoniae* was most common (32.5%), followed by pneumococcus (12.6%), *C pneumoniae* (8.9%), influenza (7.4%), *H influenzae* (6.6%), and then Gram-negative bacilli and Legionella. In many of the more recent studies, atypical pathogen infections are common, often as coinfection with bacterial pathogens. In addition, the atypical organisms are seen not only in young and healthy adults, but also in older patients, particularly *C pneumoniae* and Legionella. When atypical pathogens occur as part of a mixed infection, the outcome may be more complex and length of stay longer than if a single organism is causing infection. The elderly may have different pathogens than younger patients, with a higher incidence of infection with *H influenzae* and enteric Gram-negative organisms.

In general, the pathogens causing CAP vary in relation to specific patient factors. The American Thoracic Society (ATS) has categorized patients into four groups, each with its own list of likely pathogens (Fig 1 and Tables 1-5), by assessing illness severity (mild, moderate, or severe), the place of therapy (inpatient or outpatient), and the presence of cardiopulmonary disease and or modifying factors. Modifying factors (Table 1) are clinical conditions that put the patient at risk for infection with specific pathogens such as drug-resistant pneumococci, enteric Gram-negative organisms, and *P aeruginosa*. For all groups, the most common pathogen is pneumococcus, and therapy for CAP should always provide adequate coverage for this

Table 1—*Modifying Factors That Increase the Risk of Infection With Specific Pathogens*

Penicillin-resistant and drug-resistant pneumococci
Age > 65 years
β-Lactam therapy within the past 3 months
Alcoholism
Immunosuppressive illness (including therapy with corticosteroids)
Multiple medical comorbidities
Exposure to a child in a daycare center
Enteric Gram-negative organisms
Residence in a nursing home
Underlying cardiopulmonary disease
Multiple medical comorbidities
Recent antibiotic therapy
P aeruginosa
Structural lung disease (bronchiectasis)
Corticosteroid therapy (> 10 mg prednisone/d)
Broad-spectrum antibiotic therapy for > 7 d in the past month
Malnutrition

Table 2—*Outpatient CAP With No Cardiopulmonary Disease and No Modifying Factors*

Probable organisms
S pneumoniae
C pneumoniae (alone or as mixed infection)
M pneumoniae
H influenzae
Viruses
Miscellaneous
Moraxella catarrhalis, Legionella spp, *M tuberculosis*, endemic fungi
Therapy
Macrolide (azithromycin or clarithromycin)
—or—
Doxycycline

Table 3—*Outpatient CAP With Cardiopulmonary Disease and/or Modifying Factors*

Probable organisms
S pneumoniae (including PRSP)
Atypical pathogens such as *M pneumoniae* or *C pneumoniae*, alone or as mixed infection
H influenzae
Viruses
Enteric Gram-negative bacilli
Miscellaneous
M catarrhalis, Legionella spp, *M tuberculosis*, endemic fungi
Therapy
Selected β-lactam (cefpodoxime, cefuroxime, high-dose ampicillin, amoxicillin/clavulanate)
—plus—
Macrolide or doxycycline
—or—
Antipneumococcal quinolone *alone*

organism. In young, healthy persons, viruses and atypical pathogens are also common, but *H influenzae* is a particular concern in cigarette smokers, even in the absence of COPD. In the elderly and chronically ill, *H influenzae* (10 to 20% of cases) and enteric Gram-negative bacteria (20 to 40% of cases) are common organisms, but anaerobes must also be considered in those at risk for aspiration due to impaired consciousness or altered swallowing reflexes. In severe CAP, pneumococcus is the most common organism, but studies have also found Legionella, *H influenzae*, and enteric Gram-negative organisms to be important organisms. *P_aeruginosa* has been identified from the respiratory tract cultures of 5 to 15% of all patients with severe CAP.

While this categorization is useful in suspecting certain pathogens when other specific clues are absent, there are some epidemiologic findings that point to the presence of specific pathogens. *Legionella pneumophila* should be considered in the late summer and with exposure to contaminated water sources (cooling towers, air conditioning, saunas); *Coxiella burnetii* infection (Q fever) can follow exposure to infected cats, cattle, sheep and goats. Exposure to turkeys, chicken, and psittacine birds can lead to infection with *Chlamydia psittaci*, while contaminated bat caves may lead to histoplasmosis. Immigrants from Asia, India, or Central America should always be evaluated for tuberculosis, and melioidosis should be considered in patients who have traveled to Southeast Asia. Other epidemiologic associations with specific pathogens are listed in Table 6.

Table 4—*Hospitalized Patients With CPAP*

Cardiopulmonary disease and/or modifying factors
- Probable organisms
  - *S pneumoniae* (including PRSP)
  - *H influenzae*
  - Atypical pathogens such as *M pneumoniae* or *C pneumoniae*, alone or as mixed infection
  - Aerobic Gram-negative bacilli
  - Legionella spp
  - Respiratory viruses
  - Miscellaneous
    - *S aureus, M catarrhalis, M tuberculosis*, endemic fungi

Therapy
- Selected β-lactam with antipneumococcal activity (ceftriaxone, cefotaxime, ampicillin/sulbactam, high-dose ampicillin), IV
- —plus—
- Macrolide (choose oral or IV) *or* doxycycline (choose oral or IV)
- —or—
- Antipneumococcal quinolone *alone*, IV

Patients with no cardiopulmonary disease and no modifying factors
- Probable organisms
  - *S pneumoniae*
  - *H influenzae*
  - *M pneumoniae*
  - *C pneumoniae*
  - Mixed infection (bacteria plus atypical pathogen)
  - Viruses
  - Legionella spp
  - Miscellaneous
    - *M tuberculosis*, endemic fungi, *P carinii*

Therapy
- IV azithromycin alone
- If patient is allergic or intolerant to macrolide: doxycycline and a β-lactam, *or* monotherapy with an antipneumococcal fluoroquinolone

Table 5—*Hospitalized Patients With Severe CAP*

Patients with no pseudomonal risk factors

Probable organisms
- *S pneumoniae* (including PRSP)
- Legionella spp
- *H influenzae*
- Enteric Gram-negative organisms
- *S aureus*
- *M pneumoniae* or *C pneumoniae*
- Respiratory viruses
- Miscellaneous
  - *M tuberculosis*, endemic fungi

Therapy
- Macrolide *or* antipneumococcal quinolone
- —plus—
- Selected β-lactam with antipneumococcal activity (ceftriaxone, cefotaxime, ampicillin/sulbactam)

Patients with pseudomonal risks

Probable organisms
- *S pneumoniae* (including PRSP)
- Legionella spp
- *H influenzae*
- Enteric Gram-negative organisms
- *S aureus*
- *M pneumoniae* or *C pneumoniae*
- Respiratory viruses
- Miscellaneous
  - *M tuberculosis*, endemic fungi

Therapy
- Ciprofloxacin *plus* antipseudomonal, antipneumococcal β-lactam (imipenem, meropenem, cefepime, piperacillin/tazobactam)
- —or—
- Nonpseudomonal quinolone (levofloxacin, gatifloxacin, moxifloxacin) or macrolide *plus* antipseudomonal, antipneumococcal β-lactam (imipenem, meropenem, cefepime, piperacillin/tazobactam) *plus* aminoglycoside

Comments About Specific Pathogens

Pneumococcus

Pneumococcus is a Gram-positive diplococcus, with 85% of cases caused by 23 of the 84 serotypes. Commonly preceded by viral illness, it may cause lobar or bronchopneumonia. Pneumococcus is a common infection in those with asplenia, multiple myeloma, heart failure, alcoholism. The current vaccine includes 23 serotypes. Controversy about vaccine efficacy shows that it is safe, but may not be effective in the chronically ill. Case-control methodology has been used to show efficacy.

Penicillin-resistant *Streptococcus pneumoniae* (PRSP) is becoming a problem in some areas. In the United States, > 40% of pneumococci are penicillin-resistant, with resistance rates varying widely from region to region. Most have intermediate (penicillin minimum inhibitory concentration [MIC] ≥ 0.12 mg/mL but < 2.0 mg/L) rather than high-level resistance (penicillin MIC ≥ 2 mg/L). The clinical relevance of *in vitro* resistance is debated, but there are data to show an increased risk of death if patients have organisms with a penicillin MIC of ≥ 4 mg/L, which is currently an uncommon occurrence. Resistance is rarely a *de novo* event and is uncommon in low-risk patients, but rather is seen in immunosuppressed and chronically ill patients, especially if they have received a β-lactam antibiotic in the preceding 3 months; however, cases of epidemic transmission of resistant organisms have been reported. Other risk factors for PRSP include age > 60 years, alcoholism, and multiple medical comorbidity.

The mortality rate of hospitalized patients with pneumococcal CAP exceeds 20%, but is related to the status of the patient's immune defenses and overall health and not whether the organism is penicillin-resistant. Although most studies have shown that patients with penicillin-resistant organisms have the same mortality rate as patients who are infected with penicillin-sensitive organisms, those with very high levels of resistance may have an increased risk of death. Penicillin resistance may mean multidrug resistance, and there is a high coincidence of macrolide and trimethoprim-sulfamethoxazole resistance among penicillin-resistant pneumococci. Although quinolone resistance is uncommon for pneumococci, the less active agents, ciprofloxacin and levofloxacin, have been associated with failures of therapy due to resistance, especially if patients have received recent therapy with a quinolone.

Risk factors for mortality include the presence of bacteremia, the finding of bronchopneumonia

Table 6 — *Epidemiologic Conditions Related to Specific Pathogens in Patients With CAP*

Condition	Commonly Encountered Pathogens
Alcoholism	*S pneumoniae* (including PRSP), anaerobes, Gram-negative bacilli
COPD/smoker	*S pneumoniae, H influenzae, M catarrhalis*, Legionella
Nursing home residency	*S pneumoniae*, Gram-negative bacilli, *H influenzae, S aureus*, anaerobes, *C pneumoniae*
Poor dental hygiene	Anaerobes
Epidemic Legionnaire's disease	Legionella species
Exposure to bats	*Histoplasma capsulatum*
Exposure to birds	*C psittaci, Cryptococcus neoformans, H capsulatum*
Exposure to rabbits	*Francisella tularensis*
Travel to Southwestern United States	Coccidioidomycosis
Exposure to farm animals or parturient cats	*C burnetii* (Q fever)
Influenza active in community	Influenza, *S pneumoniae*, *S aureus*, *H influenzae*
Suspected large-volume aspiration	Anaerobes, chemical pneumonitis, or obstruction
Structural disease of lung (bronchiectasis, cystic fibrosis, etc.)	*P aeruginosa, P cepacia*, or *S aureus*
Injection drug use	*S aureus*, anaerobe, tuberculosis
Endobronchial obstruction	Anaerobes
Recent antibiotic therapy	Drug-resistant pneumococci, *P aeruginosa*

rather than lobar consolidation, and the presence of multiple comorbid illnesses. Regardless of resistance pattern, therapy for pneumococcus with high-dose penicillin (2 million units every 4 h) or a third-generation cephalosporin (cefotaxime or ceftriaxone) is adequate for invasive pulmonary disease, provided that CNS involvement is not present. The incidence of penicillin resistance is rising in certain communities, and a knowledge of the frequency of the problem and of local antimicrobial susceptibilities is necessary to assure adequate initial antibiotic therapy because some agents, such as trimethoprim-sulfamethoxazole, are increasingly ineffective against pneumococci. The new fluoroquinolones may represent appropriate empiric therapy for patients with suspected resistance. If they are used, there are differences in activity against pneumococci: levofloxacin is less active than gatifloxacin or moxifloxacin.

L pneumophila

A weakly staining Gram-negative organism, Legionella is a water-borne organism. It should be suspected in all patients with severe CAP, and in other patients based on a careful epidemiologic evaluation. Increased risk is present in those who are immunocompromised, have malignancy, smoke, have chronic lung disease, or are > 50 years old. There is no constellation of clinical signs that is specific for Legionella infection. In addition to respiratory symptoms, patients may have confusion, diarrhea, elevated results on liver function tests, hyponatremia, and relative bradycardia.

Legionella is a commonly identified pathogen in patients with severe CAP, but its overall incidence is uncertain. Unless careful diagnostic testing is done, underestimation of its frequency is likely. Sputum samples that grow Legionella often have few polymorphonuclear cells and may be discarded by microbiology laboratories. Most cases cannot be diagnosed by a single immunofluorescent antibody titer (often negative at the time of the acute illness), and are only recognized if acute and convalescent serum titers are examined for a fourfold rise. The urinary antigen is a more sensitive single test, but is specific only for infection with *L pneumophila* serogroup I.

M pneumoniae

CAP caused by *M pneumoniae* is usually a mild illness but can be severe, with complications including hemolytic anemia, myocarditis, hepatitis, cold agglutinins, and meningoencephalitis. Diagnosis is made by serology.

S aureus

S aureus can cause CAP, particularly when bacterial pneumonia complicates influenza, or when right-sided endocarditis or cavitary lung lesions are present. *S aureus* is also seen after influenza and with chronic lung disease. It may lead to cavities (pneumatoceles). Empyema is common.

C pneumoniae

C pneumoniae (the TWAR agent) is a common pathogen in young adults with tracheobronchitis and/or pneumonia, and often leads to a syndrome of "adult croup." The role of *C pneumoniae* as a respiratory pathogen is uncertain, with some studies suggesting that it functions as a copathogen more often than as a single agent. Confusion results because the organism can be isolated along with other pathogens, its clinical features cannot be differentiated from those of pneumonia caused by other organisms, and patients can recover without specific therapy. One recent study has shown that it can occur in the elderly, including those who reside in nursing homes, and it may spread from person to person. The mortality rate can be high in certain populations, and it may lead to severe forms of CAP.

Aspiration/Lung Abscess

Aspiration may involve acid (chemical pneumonitis), inert liquids or particulate matter (suffocation or postobstructive pneumonia), or oropharyngeal bacteria (aspiration pneumonia or lung abscess). Aspiration pneumonia often is polymicrobial, involving anaerobes; it may cavitate, and can be an indolent infection that is confused with malignancy. If lung abscess is seen in an edentulous patient (no mouth anaerobes), consider lung malignancy, a foreign body, or a GI source of chronic aspiration (esophageal diverticulum). The cavity usually has an air-fluid level and is > 2 cm. Cavities

from bacterial infection tend to be thick-walled, with a ragged inner lining. Lung abscess cavities usually have an air-fluid level. Tuberculosis cavities, by contrast, tend to be thin-walled and air-filled (without an air-fluid level), with a smooth inner wall. Aspiration pneumonia occurs in the superior segment of the lower lobe or the posterior segments of the upper lobe if aspiration occurs when supine, and in the lower lobe if aspiration occurs when upright. Patients with aspiration risks who also have poor dentition, a lower lobe infiltrate and pleural or chest wall involvement should be considered, possibly actinomycosis.

Influenza

Influenza can be complicated by pneumonia. It is caused by an RNA virus, with types A and B. Type A infection is generally more severe. The vaccine is trivalent and directed at both types of influenza; it reduces mortality from respiratory illness. Amantidine and rimantadine are active against only type A. The new antiviral drugs oseltamivir and zanamivir are active against both influenza A and B. Fall and early spring are peak seasons for epidemics. Attack rates are not increased in the elderly, but mortality rates are. Pneumonia may be viral or secondary bacterial. The latter occurs as the patient is improving from the initial infection, and is most commonly due to pneumococcus, *S aureus*, *H influenzae*, or Gram-negative pathogens. New interest in diagnosing influenza has come with the advent of the neuraminidase inhibitors zanamivir and oseltamivir. The former is given as a dry powder inhaler, and the latter as a pill.

Others

In HIV-positive patients, pneumococcus and *H influenzae* are common, but CAP with *P aeruginosa* has also been reported, and infection with *Pneumocystis carinii* and *M tuberculosis* must always be considered.

A newly described pathogen is the hantavirus, carried by rodents and first identified in the Four Corners area of New Mexico in May 1993. The hantavirus pulmonary syndrome is life-threatening and characterized by fulminant respiratory failure after a brief prodromal illness with symptoms of fever, myalgia, cough, dyspnea, GI symptoms, and headache. Patients are generally tachypneic and hypotensive with rapidly progressive pulmonary edema. Mortality is high, with only nonspecific and supportive therapy available (Fig 2).

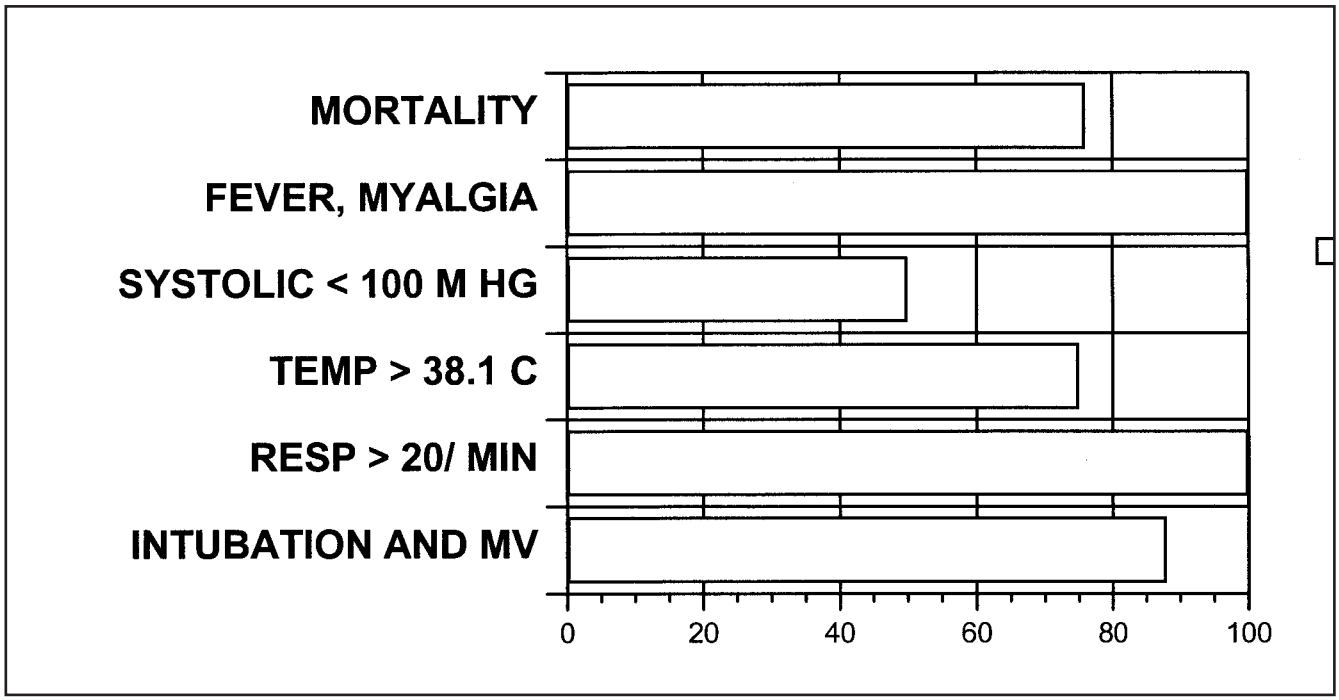

Figure 2. Characteristics of Hantavirus pulmonary syndrome. (Adapted from N Engl J Med 1994; 330:949-955.)

Diagnostic Evaluation

Because of limited yield, extensive diagnostic testing is not indicated for most CAP patients. However, certain tests can help to determine the severity of illness and presence of extrapulmonary complications. Blood cultures are positive in only 15% of patients, but provide both therapeutic and prognostic information. Controversy about the value of sputum Gram stain and culture continues, but a sputum culture alone is not a reliable way to identify the etiologic pathogen for CAP. It is clear that if diagnostic testing is done, it should be done promptly, as a > 8-h delay in antibiotic administration after coming to the hospital is associated with increased mortality. Sputum culture should be reserved for situations when an unusual or drug-resistant pathogen is suspected, particularly if the patient has not responded to initial empiric therapy. Limitations to the use of Gram stain include the following: not all patients are able to produce an adequate specimen (> 25 polymorphonuclear cells/low-power field, < 10 squamous cells/low-power field), the stain is often interpreted by technicians who are unfamiliar with the clinical circumstances, and results are often negative if the patient has taken antibiotics. In addition, a Gram stain can be either sensitive or specific, but not both; if used, it probably should be used for its specificity. The finding of any Gram-positive diplococcus is very sensitive for finding samples that will grow pneumoccus, but the finding is not very specific. On the other hand, the finding of a predominance of Gram-positive diplococci is more specific, but of course less sensitive.

An extensive diagnostic evaluation can also be useful when an unusual pathogen (*eg*, an endemic fungus, *C psittaci*) is suspected. Serologic testing is not routinely indicated, and should be reserved for patients not responding to treatment and for epidemiologic studies. Most serologic tests are positive when there is a fourfold rise in titer, and this necessitates the collection of convalescent titers, as acute testing is rarely positive. Bronchoscopy and transtracheal aspiration are not usually indicated for CAP patients, but are of value in HIV-positive or other immunosuppressed patients. Patients with severe CAP often undergo an extensive diagnostic evaluation, but studies have not shown a benefit from having a specific etiologic diagnosis. When a patient with CAP is not responding to initial empiric therapy, a re-evaluation is needed, which is directed at identifying noninfectious processes that mimic pneumonia, unusual or drug-resistant organisms, and both infectious and noninfectious complications of pneumonia. Diagnostic studies in this setting may include bronchoscopy with cultures, CT scanning of the chest, and possibly open lung biopsy, but the latter has its greatest value if a noninfectious process is suspected (bronchiolitis obliterans with organizing pneumonia, pulmonary vasculitis, etc).

The classification of the clinical presentation into "typical" and "atypical" patterns is generally of little use for predicting the microbial etiology. Not only are the clinical features caused by specific organisms not diagnostic, but some organisms, such as Legionella, lead to a clinical picture that overlaps both patterns. Clinical features usually do not accurately predict etiology because certain patient populations, particularly the elderly and chronically ill, often have an inadequate response to infection. An elderly patient with a virulent bacterial CAP may present with confusion, incontinence, falling, or worsening of a comorbid illness, rather than with fever, respiratory symptoms, and other features of the "typical" pneumonia syndrome.

Therapy

Based on the likely organisms, therapy will differ for each of the four patient subsets with CAP. Young, healthy patients with mild to moderate illness and no cardiopulmonary disease and no modifying factors should be treated with a macrolide, or tetracycline as a second choice (Table 2). The newer macrolides, azithromycin and clarithromycin, can be used and require less frequent daily dosing than erythromycin. If the patient is a cigarette smoker at risk for *H influenzae* infection, use of azithromycin or clarithromycin is suggested, as these drugs are currently approved for mild pneumonia due to this organism. Mild to moderate CAP in patients with cardiopulmonary disease and/or modifying factors should be treated with a selected β-lactam, combined with a macrolide, or alternatively with an antipneumococcal quinolone alone (Table 3). Recent data show that atypical pathogen coinfection is common enough that all patients should be treated for these organisms, using either a quinolone alone, or a macrolide added to a β-lactam. In general, trimethoprim-sulfamethoxazole is no longer a useful therapy because of the increased

incidence of pneumococcal resistance to this agent. The new fluoroquinolones (levofloxacin, gatifloxacin, and moxifloxacin) are monotherapy options for complicated outpatients, and cover Gram-positive organisms, Gram-negative organisms, and atypical pathogens, and are active against penicillin-resistant or -sensitive pneumococci.

For hospitalized patients with nonsevere CAP who do not have cardiopulmonary disease or modifying factors (such patients are rarely admitted), therapy should be with an IV macrolide alone (such as azithromycin) (Table 4). For the hospitalized patient with cardiopulmonary disease and/or modifying factors, a third-generation cephalosporin (cefotaxime, ceftriaxone, ampicillin/sulbactam, high-dose ampicillin) is indicated, combined with an oral or IV macrolide (or tetracycline) or, alternatively, with a new antipneumococcal quinolone alone (levofloxacin, gatifloxacin, moxifloxacin).

Patients with severe CAP (Table 5) should be considered for admission to an ICU and require a more aggressive therapeutic approach. Severe CAP has no uniform definition, but it is characterized by the presence of septic shock or the need for mechanical ventilation; or, alternatively, by at least two of the following three factors: systolic BP <90 mm Hg, PaO_2/fraction of inspired oxygen ratio <250, or multilobar pneumonia. Other criteria that suggest severe infection include respiratory rate >35/min, increase in the size of lung infiltrates by $>50\%$ in 48 h, oliguria, or acute renal failure. The role of the ICU in severe illness has been debated, but the ICU probably has its greatest value if used early in the course of severe disease.

Pathogens that lead to severe CAP are distinct, and slightly different from those seen in other populations. They include pneumococcus, Legionella, and enteric Gram-negative bacilli. Several studies have demonstrated that when initial empiric therapy was directed at these organisms and accompanied by a prompt clinical response, outcome was better than if ineffective therapy was used. In these studies, identification of the pathogen has not led to an improved outcome, raising questions about the value of extensive diagnostic testing even in these critically ill patients. For patients with severe CAP, an IV macrolide or quinolone should be combined with additional agents, the type and number being dictated by the presence of pseudomonal risk factors (Table 5).

For hospitalized patients who improve with initial therapy, an early switch to oral antibiotics is appropriate, and may not only shorten length of stay, but improve overall outcome. Some newer protocols have evaluated the use of combined IV and oral therapy on admission, and in some moderately ill patients, oral therapy may be as effective as IV therapy. Criteria for early oral therapy include the absence of fever on at least two consecutive determinations, the absence of an unstable medical illness, a declining white blood cell count, improvement in cough and dyspnea, and the ability to take oral medications. In general, patients who receive effective therapy will improve in 48 to 72 h, but the patient who does not respond to treatment should undergo an extensive diagnostic evaluation to identify unusual or drug-resistant pathogens, noninfectious mimics of pneumonia (vasculitis, bronchiolitis obliterans with organizing pneumonia), and complications of pneumonia. In the patient who is responding to therapy, radiographic resolution can be slow, with only 50% of a young, healthy population exhibiting radiographic clearing within 2 weeks. Slower resolution is seen in patients with bacteremia, advanced age, multilobar involvement, or underlying COPD.

Vaccination

The mainstay of CAP prevention is vaccination with both the pneumococcal and influenza vaccines. Pneumococcal vaccine should be given to all patients >65 years old and to patients, regardless of age, who have chronic heart, lung, and other medical illnesses. Patients who are asplenic and those with hematologic malignancy or HIV infection should also be vaccinated. Hospital-based immunization with pneumococcal vaccine has been suggested for the majority of patients admitted for any diagnosis, because as many as 60% of all patients with CAP have been hospitalized for some reason in the preceding 4 years. The current Advisory Committee on Immunization Practices recommendation is to repeat pneumococcal vaccination after 5 years in patients who are likely to have experienced a rapid decline in antibody concentrations. These include patients with chronic renal failure, organ or bone marrow transplant recipients, and patients at risk for fatal infection, particularly those who are asplenic.

Influenza vaccination reduces hospital admissions and mortality rates if administered before an outbreak. Repeated influenza vaccination in elderly patients is both safe and effective in preventing influenza illness and its complications. In healthy adults, the influenza vaccine can reduce the incidence of upper respiratory illness; in a nursing home population, it can reduce hospitalization rates, pneumonia rates, and mortality. Antiviral therapy with amantadine or rimantidine, which are active only against influenza A virus, or oseltamivir or zanamivir (active against influenza A and B) is used to supplement vaccination in immunodeficient patients. Antiviral therapy is indicated during an influenza outbreak in a closed environment (such as a nursing home) for all unvaccinated high-risk persons for ≥ 2 weeks following the late administration of vaccine. New studies with topical antiviral agents are promising and these agents may have a role in the future.

Annotated Bibliography

Atlas SJ, Benzer TI, Borowsky LH, et al. Safely increasing the proportion of patients with community-acquired pneumonia treated as outpatients: an interventional trial. Arch Intern Med 1998; 158:1350-1356

The prognostic scoring index of Fine (from the PORT study) is the recommended basis for deciding the need for admission for CAP in the Infectious Diseases Society of America guidelines. This study, involving 826 patients presenting to the emergency room with CAP, is a prospective evaluation of the utility of this approach,. All patients without a definite need for hospitalization were excluded, and a prognostic scoring index (PSI) was calculated for the remainder. Then the score was provided to the emergency room doctor, along with support services for outpatient care of low-risk patients; the impact of this intervention on the admission decision was observed. Results were compared with those in historical control patients managed without knowledge of the PSI. Of the 826 patients evaluated, only 166 were low-risk enough to be eligible for intervention, indicating the relatively limited impact that the PSI could have had on the admission decision. In this group of 166 low-risk patients (Fine risk groups I to III), 45% were in risk group I, 24% in group II, and 31% in group III. The data were compared with that from patients studied in a previous year; these historical control subjects numbered 147 and had a similar distribution among risk groups. In the intervention period, 57% of low-risk patients were discharged, vs only 42% in the control period (p = 0.01), and the increased discharge rate was seen in all risk groups. Among the 94 patients who were discharged in the intervention period, 8 (9%) required admission to the hospital within 4 weeks, and 5 of these admissions were clearly related to pneumonia (all within 2 days). In the control period, no patient who was discharged required admission. Interestingly, 3 of 72 patients who were admitted during the intervention period and were "low-risk" required ICU care. In the intervention period, patient satisfaction with the discharge decision was 71%, compared with 90% in the control period.

These findings raise questions about the usefulness of a prognostic scoring system to define the need for hospital admission for CAP. The intervention can be viewed as having very limited benefit: Even though more patients were discharged when the PSI was used, outpatient therapy failed in more of them than during the control period, some low-risk patients needed intensive care, and patient satisfaction was reduced when the intervention was applied.

Bartlett JG, Breiman RF, Mandell LA, et al. Community-acquired pneumonia in adults: guidelines for management. Clin Infect Dis 1998; 26:811-838

New and comprehensive guidelines for CAP, from the Infectious Diseases Society of America, that differ in several ways from the ATS guidelines.

Duchin JS, Koster FT, Peters CJ, et al. Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. N Engl J Med 1994; 330:949-955

This report describes the clinical and pathologic findings of the first 17 patients with the hantavirus pulmonary syndrome. The mean age of patients was 32.2 years, and the case fatality rate was 76%, with 88% of patients developing rapidly progressive noncardiogenic pulmonary edema. Most patients had fever, myalgias, and cough or dyspnea along with GI symptoms and headache. Although hantavirus is not a new organism, this is the first description of a pulmonary syndrome resulting from this agent.

Ewig S, Ruiz M, Mensa J, et al. Severe community-acquired pneumonia: assessment of severity criteria. Am J Respir Crit Care Med 1998; 158:1102-1108

Although the original ATS guidelines for CAP defined an entity termed "severe CAP," recent observations have suggested that this definition was overly inclusive, and that many patients who fit the definition did not actually need ICU admission. In this study of 395 patients, a modified rule for severe illness was derived from the ATS definition, because that definition (using only a single criterion for severe illness) had a specificity of only 32%. The modified rule defined the need for ICU admission as the presence of two of three "minor" criteria (systolic BP < 90 mm Hg, multilobar infiltrates, Pa_{O_2}/fraction of inspired oxygen ratio < 250) or one of two "major" criteria (need for mechanical ventilation or septic shock). This modified

definition had a sensitivity of 78%, a specificity of 94%, and a negative predictive value of 95%.

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

Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. JAMA 1996; 275:134-141

A meta-analysis of factors predicting mortality in CAP was conducted using 137 references examining 33,148 patients in 127 study cohorts. The data provide an excellent view of the epidemiology of CAP, broken down into relevant outpatient and inpatient subsets. The predictors of mortality are identified and the impact of bacteriology on outcome is reported. By virtue of the number of patients examined, this report is a state-of-the-art summary of the mortality impact of CAP and its determinants.

Kauppinen MT, Saikku P, Kujala P, et al. Clinical picture of *Chlamydia pneumoniae* requiring hospital treatment: a comparison between chlamydial and pneumococcal pneumonia. Thorax 1996; 51:185-189

Lieberman D, Schlaeffer F, Boldur I, et al. Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year prospective study of 346 consecutive patients. Thorax 1996; 51:179-184

In this prospective study of 346 hospitalized patients with CAP conducted in Israel, a surprisingly high incidence of atypical pathogen infection was found in the context of identifying an etiologic diagnosis in 80.6% of all patients, a far greater percentage than in many similar studies. The most commonly identified pathogen was pneumococcus, but M pneumoniae *was found in 29.2%,* C pneumoniae *in 17.9%, and Legionella in 16.2%. The high frequency of atypical pathogens can be explained by the careful serologic testing done and by the fact that more than one pathogen was identified in 38.4% of all patients. Atypical pathogens were seen in patients of all ages, and* C pneumoniae *was found more in older patients than in those <55 years old. The implications of these findings for therapy are uncertain since only about half of the patients with atypical pathogens received specific therapy. One possible role of atypical pathogens that is discussed is as agents that potentiate the role of bacterial organisms.*

Marrie TJ, Peeling RW, Fine MJ, et al. Ambulatory patients with community-acquired pneumonia: the frequency of atypical agents and clinical course. Am J Med 1996; 101:509-515

This is one of the few studies that has carefully examined the bacteriology of CAP in outpatients. A total of 149 adults with radiographic pneumonia were prospectively evaluated with careful serologic testing, and an etiologic diagnosis was made in 49.7%. The most commonly identified pathogen was M pneumoniae *(22.8%), followed by* C pneumoniae *(10.7%) and other atypical agents. Overall, an atypical pathogen was identified as the etiologic pathogen in >45% of all ambulatory patients, and those with this diagnosis had similar clinical features on presentation and a similar clinical course as patients without an established etiologic diagnosis.*

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

Metaly JP, Schulz R, Li Y-H, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. Arch Intern Med 1997; 157: 1453-1459

Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. Am J Respir Crit Care Med 1995; 152:1309-1315

In a 1-year prospective study, 385 patients with CAP were evaluated at an inner-city hospital. The study is unique because both HIV-infected and nonimmunosuppressed patients were evaluated and the impact of immune status on bacteriology was examined. In the 205 non-HIV-infected patients, pneumococcus was the most common pathogen, while H influenzae, *Gram-negative bacilli, and atypical pathogens were the next most frequently identified causes of CAP, but no diagnosis was found in 37%. The distribution of pathogens was such that the authors concluded that the ATS guidelines for CAP were appropriate for the population that they treated, and they endorsed the selective (rather than routine) use of macrolide therapy for hospitalized patients with CAP.*

Mundy LM, Oldach D, Autwaerter PG, et al. Implication for macrolide treatment in community-acquired pneumonia. Chest 1998; 113:1201-1206

Controversy about the role of atypical pathogens in CAP continues, and the findings of this study argue that these organisms are uncommonly present, but if identified, are often part of a mixed infection. The authors evaluated 385 patients with CAP admitted to the hospital during a 1-year period with extensive diagnostic testing for an etiologic diagnosis, including sputum cultures, serologic testing, direct fluorescent antibody testing of sputum samples for Legionella, and urinary antigen for Legionella. Although the authors tested all patients with some of the methods, acute and convalescent titers for Chlamydia were collected in very few patients, and only half underwent these studies for Mycoplasma and Legionella. Of this group, atypical pathogens were identified in only 29 patients; in 16 of the 29 patients, this was part of a mixed infection, whereas mixed infection occurred in <10% of patients who were not infected with atypical pathogens. When clinical and radiographic features were examined, there was

no distinctive pattern for patients who had atypical pathogens compared with those who had conventional bacterial pathogens. Of patients with atypical pathogens, only 4 received appropriate therapy, and no patient without specific therapy against these pathogens died. These findings led the authors to conclude that macrolide therapy is not routinely needed for patients with CAP.

Nava JM, Bella F, Garau J, et al. Predictive factors for invasive disease due to penicillin-resistant *Streptococcus pneumoniae*: a population-based study. Clin Infect Dis 1994; 19:884-890

A prospective study of 374 patients with invasive pneumococcal infection, 21% of whom had penicillin resistance. Intermediate-level resistance, present in 17% of patients, was more common than high-level resistance (4%). Risk factors for intermediate-level resistance were identified: underlying immunosuppressive illness, previous hospitalization, use of β-lactam antibiotics within the preceding 3 months, and nosocomial acquisition of infection. Only the previous use of β-lactam therapy was found to be a risk factor for high-level penicillin resistance.

Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired lower respiratory tract infections: diagnosis, assessment of severity, antimicrobial therapy and prevention. Am J Respir Crit Care Med 2001; 163:1730-1754

This document reviews the literature relevant to the management of CAP and presents an empiric approach to management based on an assessment of severity of illness, place of therapy (inpatient or outpatient), and the presence of cardiopulmonary disease and/or modifying factors. There is also a discussion of the bacteriology of CAP, the recommended approach to diagnostic testing, criteria for hospitalization and for admission to the ICU, and an approach to evaluating the patient who has not responded to initial empiric therapy.

Pallares R, Linares J, Vadillo M, et al. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. N Engl J Med 1995; 333:474-480

The results of a 10-year prospective study of 504 adults with invasive pneumococcal disease in Spain are presented, reporting an incidence of penicillin resistance approaching 30%. Factors associated with mortality were examined and the authors found that penicillin resistance per se *was not associated with an enhanced risk of dying. Adequate outcome was achieved, even for resistant strains, with the use of high-dose penicillin or with the use of cefotaxime or ceftriaxone.*

Plouffe JF, Breiman RF, Facklam RR, et al. Bacteremia with *Streptococcus pneumoniae*: implications for therapy and prevention. JAMA 1996; 275:194-198

Ramirez JA. Switch therapy in adult patients with pneumonia. Clin Pulm Med 1995; 2:327-333

Syrjala H, Broas M, Suramo I, et al. High-resolution computed tomography for the diagnosis of community-acquired pneumonia. Clin Infect Dis 1998; 27:358-363

The purpose of this study was to compare the findings of chest radiographs and high-resolution CT (HRCT) scan of the chest in 47 patients with clinical signs and symptoms of CAP, 28 of whom were treated as outpatients. All patients had erect posteroanterior and lateral films and HRCT scanning, with each test read independently by two radiologists. All 18 patients who had pneumonia seen on radiograph were identified by HRCT. However, there were an additional 8 patients with CAP identified by HRCT, including 5 who were admitted but had normal chest radiographs. In addition, more extensive abnormalities were found on HRCT, with 16 patients having bilateral infiltrates by this technique, vs only 6 having this finding on chest radiograph. In terms of radiographic patterns, bronchopneumonia was the most common type of abnormality defined by either technique, but HRCT found consolidation less often than routine radiography.

The importance of this study relates to questioning the validity of the chest radiograph as the final decision tool for the presence of CAP in patients with acute respiratory symptoms.

Weingarten SR, Riedinger MS, Varis G, et al. Identification of low-risk hospitalized patients with pneumonia: implications for early conversion to oral antimicrobial therapy. Chest 1994; 105:1109-1115

This retrospective review of the course of CAP in 503 hospitalized patients identified a subgroup of "low-risk" individuals who could have been switched from IV to oral therapy at an early time point (day 3) and discharged on day 4. For these low-risk patients, length of stay would have been dramatically reduced, with no adverse consequences, had early oral therapy been used. Criteria for early switch to oral therapy included the absence of an obvious risk for continued hospitalization, the absence of certain high-risk pathogens, and the absence of any other life-threatening complication during hospitalization.

Notes

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