Community-acquired pneumonia: an update

DAVID P. MEEKER, MD, AND DAVID L. LONGWORTH, MD

SUMMARY Despite the discovery of new pathogens and the evolving problem of antibiotic resistance, the basic trends in community-acquired pneumonia remain remarkably constant. This article reviews the common pathogens, new pathogens, their clinical presentations, the diagnostic workup, the decision to hospitalize, antibiotic resistance, and antibiotic choices.

KEY POINTS *Streptococcus pneumoniae* is still the most common causative organism in community-acquired pneumonia (CAP). Routine microbiologic testing is not mandatory in otherwise healthy outpatients with CAP not requiring hospitalization. We do favor obtaining sputum Gram's stains, sputum cultures, and blood cultures in patients requiring hospital admission. The possibility of underlying human immunodeficiency virus (HIV) infection should be considered in young patients with bacteremic *S pneumoniae* or *S pneumoniae* pneumonia. Empiric outpatient therapy with erythromycin will often suffice for relatively healthy patients, but sicker patients may need testing, hospitalization, and parenteral therapy. In critically ill patients, in those with recognized risk factors for penicillin resistance, or in geographic areas with known endemic resistant *S pneumoniae*, vancomycin is the empiric drug of choice for patients with suspected *S pneumoniae* pneumonia. Once antibiotic susceptibilities are identified, patients should be switched to penicillin if the isolate is sensitive.

INDEX TERMS: PNEUMONIA; COMMUNITY-ACQUIRED INFECTIONS
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From the Department of Pulmonary and Critical Care Medicine (D.P.M.) and Infectious Disease (D.L.L.), The Cleveland Clinic Foundation.
Address reprint requests to D.P.M., Genzyme Corporation, 1 Kendall Square, Cambridge, MA 02139-1562.

COMMUNITY-ACQUIRED pneumonia (CAP) is an evolving category of infections that reflect changing community demographics, newly discovered organisms, improved diagnostic techniques, and changing antimicrobial sensitivity patterns. Despite the discovery of organisms such as *Legionella* and *Chlamydia pneumoniae* and the resurgence of tuberculosis, the basic trends remain remarkably constant. This review examines the epidemiology of CAP, briefly reviews pertinent new information on common pathogens, and reviews the management of CAP, including what diagnostic tests to order, which antibiotics to choose, whom to hospitalize, and when to consider an alternate diagnosis. We will focus on CAP in the immunocompetent host while emphasizing the importance of considering an underlying immunocompromised state when evaluating a patient with CAP.

EPIDEMIOLOGY

Although the law does not require physicians to report cases of pneumonia, crude estimates suggest the annual incidence is 4 million cases. Twenty percent of patients require hospitalization.[1] Pneumonia remains the sixth leading cause of death and the number-one infectious cause of death.[1] Numerous large studies have

TABLE 1
MOST COMMON CAUSATIVE ORGANISMS IN COMMUNITY-ACQUIRED PNEUMONIA*

Site	Year	No.	Most common	%	Second most common	%	Third most common	%	Unknown (%)
Edinburgh[5]	1960–1962	141	*Streptococcus pneumoniae*	44	*Haemophilus influenzae*	22	Viruses	—	38
Baltimore[5]	1965–1966	100	*S pneumoniae*	62	Viruses	12	*Mycoplasma*	3	34
Atlanta[5]	1967–1968	292	*S pneumoniae*	62	Gram–negative	20	Viruses	11	43
Milwaukee[5]	1969–1970	148	*S pneumoniae*	53	*Staphylococcus aureus*	7	*Klebsiella*	6	17
Baltimore[5]	1970–1971	144	*S pneumoniae*	47	*H influenzae*	46	*S aureus*	14	13
Nottingham[5]	1980–1981	127	*S pneumoniae*	76	*Legionella*	15	*Chlamydia psittaci*	6	3
Hartford[5]	1981	204	*S pneumoniae*	36	*H influenzae*	15	*Legionella*	14	0
Goteborg[5]	—	127	*S pneumoniae*	54	*Mycoplasma*	14	Influenza A	12	21
Nova Scotia[5]	1981–1982	138	Aspiration	15	*S pneumoniae*	9	*H influenzae*	9	44
Oreboro[5]	1982	147	*S pneumoniae*	39	*H influenzae*	5	*Mycoplasma*	5	29
Britain[5]	1982–1983	453	*S pneumoniae*	42	*Mycoplasma*	10	Influenza A	7	33
France[5]	1982–1983	274	*S pneumoniae*	12	*Legionella*	11	*Mycoplasma*	9	49
Nova Scotia[5]	1981–1984	301	Aspiration	11	*S pneumoniae*	9	*H influenzae*	6	37
Paris[5]	1983–1984	116	*S pneumoniae*	26	*H influenzae*	11	*Mycobacterium tuberculosis*	10	35
Nottingham[5]	1984–1985	236	*S pneumoniae*	36	Influenza A	6?	Other viruses	12	45
Pittsburgh[5]	1986–1987	359	*S pneumoniae*	15	*H influenzae*	11	*Legionella*	7	33
New Zealand[6]	1988	92	*S pneumoniae*	30	*Mycoplasma*	17	Influenza A	8	28
Valencia[7]	1985–1986	510	*S pneumoniae*	74	*Legionella*	70	*Mycoplasma*	22	45
Little Rock[8]	1985	154	*Legionella*	13	*S pneumoniae*	8	*Chlamydia*	8	51
Barcelona[9]	1984–1987	92	*S pneumoniae*	14	*Legionella*	13	*Mycoplasma*	6	48
Nova Scotia[10]	1981–1987	719	*S pneumoniae*	9	Aspiration	7	*Mycoplasma*	6	47

*Modified from Fang et al, reference 5

examined the epidemiology of CAP. Unfortunately, these studies have varied in types of populations, diagnostic methods, and inclusion and exclusion criteria, all of which complicate their interpretation.

The increased incidence of human immunodeficiency virus (HIV) infection and its expansion into new populations mandates that risk factors for HIV infection be sought in all patients with CAP. In addition to being vulnerable to infection with opportunistic pathogens that cause pneumonia, HIV-infected patients also have a higher incidence of CAP due to *Streptococcus pneumoniae* and *Haemophilus influenzae*.[2–4]

S pneumoniae still most common pathogen

Fang et al[5] reviewed the reports of 16 CAP case series published between 1960 and 1987 that included 100 or more patients. *Table 1* is adapted from their literature review and includes four additional studies of comparable size published recently.[6–10] Although recent reviews have stressed CAP's changing epidemiology, equally striking is the persistence of the overall basic pattern. *S pneumoniae* was the most commonly identified pathogen in 17 (85%) of the 20 series, despite the recent recognition of the *Legionella* organisms and C *pneumoniae*. Further, of six major series accruing patients after 1985, five listed *S pneumoniae* as the most frequently identified organism. However, the frequency of *S pneumoniae* pneumonia varied considerably from study to study.

The true incidence of *S pneumoniae* pneumonia likely exceeds that reported in most series, as it is diagnosed more frequently when more diagnostic tests are performed.[10,11] Studies relying on sputum cultures alone may significantly underestimate the true incidence of *S pneumoniae* pneumonia because this test lacks sensitivity. For example, in one study, *S pneumoniae* failed to grow in 45% of sputum samples from patients with documented bacteremic *S pneumoniae* pneumonia.[12]

TABLE 2
CLINICAL CONDITIONS AND LIKELY ASSOCIATED PATHOGENS

Condition	Organisms
Immunocompromised state	Opportunistic pathogens: *Pneumocystis carinii* Fungi *Mycobacterium tuberculosis* Atypical mycobacteria Cytomegalovirus
Chronic obstructive pulmonary disease	*Haemophilus influenzae* *Moraxella catarrhalis* *Streptococcus pneumoniae*
Alcoholism	Gram-negative organisms *S aureus* *M tuberculosis* *S pneumoniae* Anaerobes
Diabetes mellitus	Gram-negative organisms *Staphylococcus aureus* *M tuberculosis*
Bird exposure	*Chlamydia psittaci* Fungi
Cattle, sheep exposure	*Coxiella burnetti*
Wild animal exposure, tick bites, travel in wooded areas	*Francisella tularensis* *Yersinia pestis*

Other common pathogens

Although *S pneumoniae* was the most common pathogen in the majority of studies, a variety of other pathogens ranked second through fifth. *Legionella* species were consistently recognized in studies after 1980, and C *pneumoniae* after 1984. Because both organisms are difficult to grow in culture, their diagnosis must rely on other techniques. *Legionella* can be diagnosed by direct fluorescent antibody (DFA) testing, DNA probes, urinary antigen testing, and serologic testing; the diagnosis of C *pneumoniae* infection depends primarily on serologic testing. Influenza A, *H influenzae*, and *Mycoplasma pneumoniae* are the other organisms frequently identified. Enteric gram-negative organisms are infrequently identified, although their incidence is higher in some patient groups such as nursing-home residents[13] and patients with severe CAP.[9,14] Two studies of patients with severe CAP requiring intensive care reported a high frequency of *Legionella* infections (23% and 14% of cases) and gram-negative bacterial infections (11% and 7% of cases).[6,11] Notably, *S pneumoniae* remained the most commonly identified organism in both studies, accounting for 37% and 14% of cases.

Anaerobic infections

In most CAP series, infections with anaerobic bacteria were rarely detected. Healthy people routinely aspirate small amounts of oropharyngeal secretions, but local defense mechanisms efficiently clear most bacteria. Infection occurs when this balance is disrupted. Because the diagnosis of anaerobic pneumonia depends on invasive techniques, these infections may go unrecognized. Two studies, one using transtracheal aspiration[15] and one using protected specimen brushing[16] to obtain untainted specimens from the lower respiratory tract, identified anaerobes in 33% and 21% of samples, respectively.

Whether these numbers accurately reflect the prevalence of anaerobic infection in the broader CAP population is unknown. However, certain predisposing conditions should suggest the possibility of anaerobic infection. Sixty percent to 90% of patients with anaerobic infections have conditions associated with stasis of secretions or necrosis of tissue such as pulmonary infarction, tumors causing endobronchial obstruction, or bronchiectasis.[16] Conditions that predispose to aspiration and poor oral hygiene also increase the likelihood of anaerobic infection. It is more difficult to interpret the role anaerobes play in mixed infections: the anaerobic component may go unrecognized and the disease may be attributed solely to the aerobic pathogen.

Pathogen is often not identified

Another consistent finding in many series is the high percentage of cases for which a microbiologic diagnosis was not established. This percentage has not decreased with improved diagnostic techniques and approached 50% in four recent studies.[7–10] The number is probably even higher outside of epidemiologic studies, where evaluation is not standardized and empiric therapy is common.[17] Early empiric use of antibiotics, difficulties in diagnosing *S pneumoniae* pneumonia, and failure to obtain serologic studies during convalescence all impede microbiologic diagnosis.

Differences in populations

Differences in patient populations partly account for the variable incidence of specific infections in CAP series. Aging, chronic underlying illnesses, and local epidemiologic factors may all influence the likelihood of contracting infection with specific organisms. The initial evaluation requires careful at-

tention to risk factors that might suggest an organism other than those routinely associated with CAP (*Table 2*).

For example, the incidence of *Mycobacterium tuberculosis* infection is again increasing. The possibility of *M tuberculosis* infection should be considered in patients who have a history of tuberculosis infection or exposure and in HIV-infected patients, the homeless, and residents of nursing homes. The rising incidence of multidrug-resistant tuberculosis increases the importance of early recognition and appropriate therapy.

M pneumoniae pneumonia occurs predominantly in relatively young patients, with a peak incidence between the ages of 30 to 40, and rarely in patients older than 65 years. However, *M pneumoniae* spreads easily among household contacts; a history of multiple illnesses in the same family should raise the possibility of *M pneumoniae* regardless of patient age.[18]

Community-acquired pneumonia in the elderly

People older than 65 years, a population predicted to reach 30 million by the year 2000,[19] constitute the majority of patients with CAP. Several series that specifically examined CAP in the elderly suggest some fundamental differences between younger and older patients.[19–22] A variety of factors may explain the high incidence of CAP and associated morbidity in the elderly. Thymus involution and impaired regulatory T-cell function may produce a subtle immunodeficiency.[19,20] Mechanical factors such as a decreased cough reflex, decreased lung elastic recoil, and decreased ciliary action further impair host defenses. Aspiration of oropharyngeal contents (rather than inhalation) and contiguous or hematogenous spread of infection are the most common mechanisms leading to pneumonia in elderly patients. However, the major determinant of the increased incidence of CAP in the elderly may be concomitant diseases.

S pneumoniae remains the most commonly identified pathogen in the elderly, accounting for 18% to 60% of cases of CAP.[19,23,24] The low frequency of *S pneumoniae* in some studies has been attributed to previous use of antibiotics and reliance on sputum Gram's staining and culture. For example, Marrie et al[25] found the percentage of cases attributed to *S pneumoniae* increased from 9.4% to 27% when only patients who had sputum cultures before receiving antibiotics were considered.

Other commonly identified pathogens in the elderly include *H influenzae*, *Legionella* species, influenza viruses, and other gram-negative organisms.[24,26,27] The elderly are more likely to be colonized with gram-negative organisms, and the frequency of colonization in people older than 75 years correlates with the level of assistance with daily activities that they need.[13] In one study, elderly residents of independent living units had a 19% prevalence of colonization, compared with 37% in patients in a skilled nursing facility and 60% in comparably aged hospitalized patients.[13]

Chronic illnesses are more prevalent in the elderly, further contributing to the risk of pneumonia. Conditions frequently associated with CAP include alcoholism, diabetes mellitus, cancer, and chronic obstructive pulmonary disease (COPD). Specific organisms likely to be associated with these conditions are listed in *Table 2*. Notably, pharyngeal colonization by gram-negative bacteria is more common in alcoholics and patients with diabetes.[28] In one study, the prevalence of colonization was significantly greater among insulin-dependent diabetic patients (nine of 17, 53%) than among non-insulin-dependent patients (six of 24, 25%).[28] COPD was the most frequently identified underlying illness in a number of studies. *S pneumoniae*, *H influenzae*, and *Moraxella catarrhalis* are more likely to be identified in this patient population.

INDIVIDUAL PATHOGENS: PRESENTATION, DIAGNOSIS, AND TREATMENT

In an attempt to determine etiology on the basis of clinical presentation, physicians have grouped organisms into "atypical" and "typical" categories. Unfortunately, the clinical presentations overlap extensively, undermining the usefulness of this distinction. "Typical" pathogens include *S pneumoniae*, *H influenzae*, *M catarrhalis*, and less commonly identified gram-negative and gram-positive organisms. "Atypical" pathogens include *Legionella* species, *M pneumoniae*, *C pneumoniae*, viruses, *Coxiella burnetii*, and *Francisella tularensis*. With improved diagnostic techniques, physicians are increasingly recognizing *Legionella* species, *M pneumoniae*, and *C pneumoniae* as important treatable causes of CAP.

Legionella

The *Legionellaceae* family comprises 30 recognized species with over 50 individual serogroups. The *Legionella pneumophila* serogroups account for most in-

fections,[29] although infections with organisms other than *L pneumophila* may be more common in immunosuppressed patients.[5,8,14] The organisms are pleomorphic, faintly staining, gram-negative bacilli that grow slowly on specialized media.[30]

Legionella species were initially recognized as pathogens after an epidemic illness at an American Legion convention in 1976. Retrospective serum analysis using immunofluorescent antibody (IFA) testing subsequently demonstrated that this was not a new disease and that the organisms had been present in 1947 and had caused an epidemic in 1965.

Since 1980, *Legionella* species have consistently ranked among the five most frequent causes of CAP. In one recent study of all hospitalized pneumonia patients, *Legionella* species accounted for 22.5% of cases, compared with only 10.6% for *S pneumoniae*.[31] However, in that series, 68% of the *Legionella* cases were nosocomial infections. In most studies, *Legionella* species accounted for a much smaller percentage of CAP cases, particularly in patients with less-severe disease.

In a series of 79 outpatients with lower respiratory tract infections (bronchitis or pneumonia or both), serologic studies before and after treatment found no evidence of *Legionella* infection.[32] A 3-year prospective study of nosocomial pneumonia and of CAP requiring hospitalization used multiple diagnostic methods, including urinary antigen testing. That study found that 23 (3.4%) of 684 cases of CAP and 33 (5.9%) of 559 cases of nosocomial pneumonia were due to *Legionella* species.[33] A similar prevalence of 7% was reported in a series of 400 cases of CAP requiring hospitalization during a period of no identified outbreaks.[34] The researchers attributed the increase in prevalence of infections due to *Legionella* species at their institution (from 2.5% in the early 1980s to 7% in the late 1980s) to better diagnostic methods rather than an actual increase in *Legionella* infections.[34]

Legionella species are saprophytic water-borne bacteria. Epidemiologic evaluations have linked outbreaks to contaminated air-conditioning systems, cooling towers,[35] construction sites, and showers that aerosolize the organism.[30,36] However, the low concentration of organisms in aerosols and the apparently high organism load required to produce disease suggest a different or more complicated pathogenic process.

One hypothesis is that the organisms congregate inside amoebae, which can be aerosolized and travel long distances.[37] Another hypothesis, based on more recent evidence that *Legionella* species can colonize water distribution systems, suggests that contaminated tap water was the source of many of the outbreaks and aspiration the likely mode of transmission.[37,38] Circumstantial evidence for aspiration as the mode of transmission includes the low incidence in reported epidemics and the identical risk factors for *Legionella* pneumonia as for other bacterial pneumonias (cigarette smoking, COPD, cardiac disease, immunosuppression, and old age).

The pathogenesis of *Legionella* infection is only partially understood. *Legionella* species are intracellular pathogens that can survive and multiply in monocytes and macrophages. The release of several exotoxins and a relatively weak endotoxin contribute to its pathogenesis. The body's major defense is via cell-mediated immunity. The reported mortality rate has ranged from 10% to 46% in hospitalized patients[31,33,34,39] and may reach 80% in immunocompromised patients not treated with erythromycin.[33]

Clinical presentation. The clinical presentation may be quite variable. The incubation period ranges from 2 to 10 days. Most patients have fever and a minimally productive cough.[39] Gastrointestinal symptoms are present in 25% to 50% and should suggest possible infection with *Legionella* species.[34,39] Relative bradycardia (a heart rate of 100 or less with a temperature higher than 39.4°C) may be seen.[39] Neurologic symptoms, which may include headache and confusion, are present in 25% to 35% of patients.[34,39,40] Upper respiratory tract symptoms such as rhinorrhea and sore throat are characteristically absent.

A nonpneumonic form of legionellosis has also been described and termed "Pontiac fever," owing to its initial recognition in an outbreak in Pontiac, Michigan.[41] This illness is characterized by the sudden onset of fever, chills, headache, and myalgias and is self-limiting, even without specific therapy. Pontiac fever differs from *Legionella* pneumonia in several important ways: it has a short incubation period (1 to 2 days), is not associated with pneumonia, and resolves spontaneously.[42] The pathogenesis of Pontiac fever has been debated, but may involve exposure to nonviable organisms or certain host factors.[42]

Diagnosis. Laboratory features in *Legionella* infections may include leukocytosis, hyponatremia, hypophosphatemia, abnormal liver function test results, and hematuria.[30,34,39,40] Studies specifically comparing *Legionella* infections with *S pneumoniae* infections have not confirmed any clear differentiat-

ing clinical features.[31,34,40] Hyponatremia does occur more frequently in *Legionella* infection but is not specific to this infection and may be seen in other types of CAP.[31,34,40] Whether the laboratory abnormalities and multiorgan involvement reflect unique properties of the organism or simply that *Legionella* species are more often recognized in severe cases of pneumonia is unknown.

Radiographically, alveolar infiltrates predominate, often progressing to dense consolidation.[39] Interstitial infiltrates may be seen early but usually progress. Pleural effusions may be present, although empyema is rare.[39] The radiographic presentation does not reliably distinguish *Legionella* species from other causes of CAP.[43] However, bacteremic *S pneumoniae* pneumonia and *Legionella* pneumonia are the two forms of CAP most likely to show radiographic progression after antibiotic therapy is started.[43]

Since no gold standard exists for diagnosing *Legionella* infections, the true sensitivity of available diagnostic methods remains unknown. Rough estimates for each of the available methods are listed in *Table 3*.[29] The large variability in reported sensitivities may reflect different levels of laboratory expertise.

Although the diagnostic yield is higher in specimens obtained from the lower respiratory tract,[33] the organism can be cultured from sputum samples. Even contaminated sputum samples containing 25 or more epithelial cells per low-powered field grew the organism in eight of 17 documented cases in one study.[34] *Legionella* species do not colonize the upper respiratory tract and should be considered a pathogen when found.

Urinary antigen testing is a sensitive, rapid (usually positive within 3 days of illness onset),[35] and highly specific means of documenting infection with *L pneumophila* serogroup 1, but regrettably does not distinguish acute from remote infection, since antigenuria may persist for up to a year.[35] Moreover, the test only identifies the antigen from *L pneumophila* serogroup 1; thus, a negative test does not exclude infection with other serogroups or species. Nevertheless, in the appropriate setting, a positive test may provide useful information, especially since approximately 80% of *L pneumophila* infections are due to serogroup 1.[44]

Treatment. Adequate therapy requires an antibiotic that is active inside cells, administered long enough (generally 3 weeks).[29] Erythromycin (750 mg to 1 gram every 6 hours) is the agent of choice. Rifampin also has good intracellular penetration and can be added in severe cases at a dosage of 600 mg every 12 hours. Tetracycline is an alternative second-line agent. The new macrolides (clarithromycin and azithromycin) and the quinolones are also active against *Legionella* species, although clinical experience with them is limited.[29]

TABLE 3
COMPARISON OF SPECIALIZED TESTS FOR DIAGNOSIS OF LEGIONNAIRES' DISEASE*

Test	Sensitivity (%)	Specificity (%)
Culture		
Sputum	50–70	100
Transtracheal aspirate	90	100
Blood	20	100
Serology	70–96	96–99
Direct fluorescent antibody	25–80	96–99
Urinary antigen	75–90	100
DNA probe	50–65	95–99

*From Nguyen MLT and Yu VL, reference 29, with permission

Most patients with *Legionella* pneumonia should receive parenteral therapy at the outset, which should be continued until a clinical response is evident, generally 3 to 7 days. Immunocompromised patients may require longer courses of parenteral therapy and should receive a total of 2 to 3 weeks of antibiotic therapy.

Mycoplasma pneumoniae

M pneumoniae accounts for approximately 5% to 20% of cases of CAP, depending on the population. *M pneumoniae* pneumonia occurs predominantly in younger adults but is increasingly recognized in older people. Marrie[45] reported a 4.9% frequency (64 of 1300 cases) of *M pneumoniae* in a prospective study of CAP, of which six cases (9.3%) were in patients 65 years or older.

Infection occurs with inhalation of the organism. Enclosed population groups such as students in college dormitories, military recruits, and close family contacts may experience localized outbreaks.[18,46,47] In one such outbreak, 36 (95%) of 38 persons in six families exposed to five original patients also became infected.[18] Dissemination occurred slowly; the last infection developed 6 to 8 weeks after the index case was identified. The clinical manifestations in this outbreak were highly variable and included pneumonia (14 cases), respiratory tract infections without pneumonia (20 cases), and asymptomatic

seroconversion (2 cases). M *pneumoniae* tended to persist in the respiratory tract; 50% of those followed serially had positive culture results at 4 weeks, and one person's culture results remained positive at 10 weeks. Treatment with tetracycline failed to eradicate the organism, and cultures remained positive 2 to 6 weeks after treatment.[18]

Clinical presentation. The varied clinical manifestations of M *pneumoniae* infection include both pulmonary and extrapulmonary involvement.[46,48] Pharyngitis or bronchitis develops in most infected people; pneumonia develops in 10% to 25%. A smaller percentage remains asymptomatic despite seroconversion.[18,46] Patients with M *pneumoniae* pneumonia usually present with fever and a nonproductive or minimally productive cough; when the cough is productive the sputum is purulent in approximately 20% of cases.[48] Headache and otalgia are other common complaints, occurring in 40% to 80% and 2% to 35% of cases, respectively.

Chest radiographs classically reveal unilateral lower lobe consolidation or patchy infiltrates, although multilobe involvement is common.[43,49] Pleural effusions (present in 20% of cases) and lymphadenopathy are less common.[43,50] Most pleural effusions are small, although massive M *pneumoniae*-related effusions have been reported.

The white blood cell count may be normal or mildly elevated, with marked elevation occurring in rare, severe cases. Unfortunately, laboratory and radiographic findings do not reliably discriminate M *pneumoniae* from other common causes of CAP such as S *pneumoniae* and *Legionella* species.[43]

Extrapulmonary manifestations occur in a minority of patients with M *pneumoniae* infection and include cold agglutinin-induced autoimmune hemolytic anemia, central and peripheral nervous system disease, hepatitis, myopericarditis, arthritis, and erythema multiforme.[48,50]

Diagnosis. M *pneumoniae* can be diagnosed definitively by culturing the organism or by serologic techniques. Although the organism grows readily in broth medium, culturing it requires 7 to 10 days and is rarely clinically useful.[50] Further, the organism continues to be excreted for up to 7 months after the acute infection, decreasing the specificity of culturing for diagnosing acute infection.

The available serologic tests include a complement fixation test and a specific test for IgM antibody as measured either by indirect immunofluorescent assay or an IgM capture enzyme immunoadsorbent assay. A fourfold rise in complement fixation titer or a single titer of 1:256 or more is diagnostic. Unfortunately, complement fixation titers may remain elevated for months, making it difficult to differentiate between acute and previous exposure. The IgM assay provides an earlier, more specific result but may be negative in reinfection, in which the IgM antibody response is lacking.[51] Simultaneous measurement of IgM, IgG, and IgA specific antibody may improve diagnostic sensitivity but is rarely warranted clinically except in epidemiologic studies.[51]

Treatment. Erythromycin and the tetracyclines remain the antibiotics of choice for the therapy of mycoplasma pneumonia. Well-designed prospective studies have demonstrated that these agents shorten the duration of symptomatic illness, although viable organisms may persist in respiratory secretions despite therapy. The newer macrolides azithromycin and clarithromycin are also effective, though considerably more expensive. Therapy should be continued for at least 14 days.

Chlamydia pneumoniae

C *pneumoniae* is an obligate intracellular gram-negative bacteria first recognized as a cause of upper and lower respiratory tract infections in 1986.[52] Originally considered a strain of *Chlamydia psittaci* and designated "Taiwan acute respiratory (TWAR) agent," it is now recognized as a distinct species with only one identified strain. Epidemiologic studies suggest it accounts for approximately 10% of cases of CAP.[53] Nosocomial infection has also been reported.[54] Serologic evidence of previous infection is common: 30% to 50% of the population has a positive antibody response by early adulthood.[54] The distribution of infection is bimodal, with peaks at 8 to 9 years and 70 years.[54] Reinfection with C *pneumoniae* may also occur.[55]

Clinical presentation. The clinical presentation is usually mild and nonspecific, precluding differentiating C *pneumoniae* from other causes of CAP on clinical grounds. Most patients present with fever, a cough (which may be productive), a mildly elevated white blood cell count, and a localized radiographic infiltrate.[56] Some patients also present with hoarseness, which should suggest the diagnosis. The onset of illness may be indolent, with symptoms present for a few days to 2 weeks before presentation.[55,57] C *pneumoniae* pneumonia may be more severe in patients who already have serious chronic diseases.[56]

Epidemiologic data from a Norwegian epidemic in military recruits confirmed the high frequency of subclinical infections. Extrapolated data suggested that 49% of 500 soldiers contracted subclinical infections, while pneumonia developed in only 7%.[58]

Although the exact mechanism of spread remains unclear, man is the only known reservoir for C *pneumoniae*, and person-to-person spread is probable. C *pneumoniae* may survive on environmental surfaces for up to 30 hours, and measurable amounts may be transferred to the hands.[59] However, survival time on the hands is only 10 to 15 minutes.[59]

Diagnosis. The diagnosis of C *pneumoniae* relies predominantly on serologic studies using microimmunofluorescent tests. A fourfold or greater rise in either the IgM or IgG antibody, a single IgM titer of 1:16 or greater, or an IgG titer of 1:512 or greater is diagnostic.[54] Routine absorption of IgG should be performed before IgM testing, since the presence of rheumatoid factor may produce false-positive results.[54] IgM appears approximately 3 weeks into the illness; IgG at 6 to 8 weeks.[53] The organism is difficult to culture, although the recent discovery that the HEp-2 cell line supports growth may facilitate its isolation in culture.

The complement fixation test is genus-specific, reacting with both C *trachomatis* and *psittaci* species. Only approximately one third of patients with C *pneumoniae* have complement fixation antibody.[53] Polymerase chain reaction techniques may further facilitate the diagnosis once they become available for routine clinical use.[54]

Treatment. A number of antibiotics have in vitro activity against C *pneumoniae*, although controlled clinical trials are lacking. Doxycycline, tetracycline, and erythromycin have all shown activity. Clarithromycin, azithromycin, ciprofloxacin, and ofloxacin are alternative agents with demonstrated activity, although the optimal duration of therapy with these agents remains to be defined.[54]

Viral pneumonias

Viruses are an uncommon, albeit probably underrecognized cause of CAP in adults. Adenovirus is a recognized cause of pneumonia in military recruits, whereas influenza A is the most common cause of viral pneumonia in the general adult population.[60]

Both type A and type B influenza viruses can cause influenza. Influenza A viruses are classified into subtypes on the basis of hemagglutinin and neuraminidase antigens. Antigenic variation from year to year can lead to epidemics with dramatic increases in associated morbidity and mortality, particularly in high-risk populations (ie, people older than 65 years and those with underlying chronic illnesses).[61] Infections occur between October and March annually. Each year, influenza activity and hospitalizations for acute respiratory disease tend to peak simultaneously, underscoring the etiologic importance of the influenza virus in acute respiratory illness.[62]

Clinical presentation. Patients present with fever, myalgias, sore throat, a nonproductive cough, dyspnea, and wheezing. The chest radiograph may reveal localized patchy infiltrates or widespread interstitial infiltrates. Superimposed bacterial infection with *S pneumoniae*, *H influenzae*, or *Staphylococcus aureus* is common.

Vaccination. Yearly vaccination remains the cornerstone of prevention. The vaccine is safe and is based on an assessment of antigenic shifts in the virus. Ideally, it should be given between mid-October and mid-November, although anytime after the vaccine becomes available in September is acceptable. A concerted effort should be made to reach high-risk groups. A standing order for influenza vaccine, allowing nurses to identify and vaccinate people at risk, proved a successful strategy in one clinic, dramatically increasing the vaccination rate from 28% to 81%.[63] Influenza vaccine may also be of benefit in otherwise-healthy, working adults. A recent study demonstrated that, compared with placebo recipients, immunized healthy adults had fewer episodes of upper respiratory illness, fewer days of lost work, and fewer visits to physicians.[64]

Diagnosis. The diagnosis can be made by culturing the virus from respiratory secretions or by demonstrating a serologic conversion. Immunofluorescence of exfoliated nasal pharyngeal cells now provides a diagnosis in approximately 15 minutes, which is extremely valuable if antiviral therapy is contemplated.[65]

Treatment. Both amantadiné and its structural analog, rimantadine, provide effective prophylaxis against influenza A infections in exposed persons and can decrease the duration of symptoms and viral shedding in those infected by 1 to 2 days if given early in the illness.[66–68]

Streptococcus pneumoniae

S pneumoniae remains the most common cause of CAP, accounting for 10% to 75% of cases (*Table 1*). The organism commonly colonizes the upper respiratory tract, and pharyngeal carriage rates range

from 5% in childless adults to 25% in children and up to 60% in infants. Rates may be higher in closed populations.[69] Person-to-person spread is presumed, although the exact mechanism remains unknown.

In spite of antibiotics, mortality rates in bacteremic *S pneumoniae* pneumonia remain high. Mortality rates ranged from 23% to 45% in the years 1952 to 1984, and have not decreased in recent years.[70] The incidence of bacteremia and associated mortality is highest in the elderly, in splenectomized patients, and in those with underlying medical illnesses.[21,23,71] The classic clinical features of pneumonia may be absent in the elderly, who are more likely to present with dehydration and a change in mental status.[40]

HIV-infected people are also at risk for more severe disease. *S pneumoniae* pneumonia was the first manifestation of HIV-related illness in 10 (48%) of 22 patients in one study, and 16 (76%) of the HIV-infected patients had bacteremia.[72] The possibility of an underlying HIV infection should be considered in young patients with *S pneumoniae* bacteremia or pneumonia.

Diagnosis. Diagnosing *S pneumoniae* is hampered by the poor sensitivity and specificity of available tests. Blood cultures remain the "gold standard" but are positive in only 25% to 30% of cases. The interpretation of sputum Gram's stains and cultures is complicated by the tendency of *S pneumoniae* to colonize the upper respiratory tract and by the poor sensitivity of sputum cultures.[12] Measuring pneumococcal polysaccharide antigens may have better diagnostic sensitivity.[72,73] However, antigen from colonizing organisms and persistence of antigen from remote infections may lower this test's specificity.[74] Further research is required before these assays will be ready for routine clinical use.

Vaccination. The pneumococcal vaccine effectively prevents pneumonia in immunocompetent people. The original 14-valent vaccine has been replaced by a 23-valent vaccine, which contains noninfectious capsular polysaccharides of the most prevalent infectious serotypes, which account for more than 80% of cases of bacteremic *S pneumoniae* pneumonia. The clinical effectiveness of the vaccine is calculated at 60% to 70% in immunocompetent people, including those older than 55 years.[75]

Treatment and antibiotic resistance. Until recently, penicillin was the antibiotic of choice, and most strains demonstrated excellent susceptibility. However, since 1967, penicillin-resistant strains have become more common. More ominously, such strains have also developed resistance to other previously active antibiotics such as erythromycin, tetracyclines, and trimethoprim-sulfamethoxazole.

Penicillin resistance is defined by maximal inhibitory concentrations (MIC). Sensitive strains have an MIC of 0.1 μg/mL or less, intermediate resistant strains have an MIC of 0.1 to 1.0 μg/mL, and highly resistant strains have an MIC of 2.0 μg/mL or greater. The highest prevalences of resistant strains are found in South Africa, Eastern Europe, Spain, and Mexico. In the United States, an estimated 4% to 5% of pneumococcal strains are penicillin-resistant.[76,77]

Resistance is caused by alterations in penicillin-binding proteins as opposed to beta-lactamase production.[76] Risk factors for penicillin resistance include previous treatment with beta-lactam antibiotics and nosocomial pneumonia.[78]

Vancomycin is the antibiotic of choice for penicillin-resistant strains. Imipenem and some third-generation cephalosporins may have activity against these strains, but they should be tested individually.[76] In critically ill patients, in those with recognized risk factors for penicillin resistance, or in geographic areas in which resistant *S pneumoniae* is endemic, vancomycin is currently the empiric drug of choice for patients with suspected *S pneumoniae* pneumonia. Once antibiotic susceptibilities become available, patients should be switched to penicillin if the isolate is sensitive to it.

Haemophilus influenzae

H influenzae is a gram-negative coccobacillus that grows readily on available media. It exists in both typable—defined by the presence of a polysaccharide capsule—and nontypable forms. Pathogenicity was originally attributed only to the encapsulated form, but all forms can cause disease.[79] The reported frequency of *H influenzae* as the causative organism in CAP ranges between 4% and 46% (*Table 1*).

Clinical presentation. Most patients with *H influenzae* pneumonia have a serious underlying illness, mostly commonly COPD.[80–83] In one series of 194 cases of invasive *H influenzae* pneumonia, 47 cases (24%) occurred in adults, and 70% of the patients had bacteremia.[82] Fifty-three percent of the cases were due to *H influenzae* type B, and 47% to nontypable forms.

Diagnosis. H influenzae commonly colonizes the upper respiratory tract in both adults and children,

complicating interpretation of sputum Gram's stain and culture results. Further, sputum cultures may be insensitive, growing the organism in only 50% of bacteremic *H influenzae* pneumonia patients, similar to the yield for *S pneumoniae*.[81,83]

Treatment. Treatment is complicated by the increasing prevalence of beta-lactamase-producing strains. Sixteen of 45 isolates (36%) were ampicillin-resistant in a recent study of invasive *H influenzae*, significantly higher than the previously reported frequency of 2% to 5%.[82] Treatment with an antibiotic active against beta-lactamase-producing organisms, such as a third-generation cephalosporin, is indicated in cases of suspected *H influenzae* pneumonia or febrile tracheobronchitis.

Moraxella catarrhalis

M catarrhalis, previously considered simply a commensal microorganism found in the upper respiratory tract, is now recognized as a potential pathogen and occasional cause of CAP.[84,85] The organism is a large gram-negative diplococcus similar to *Neisseria* species. Since nonpathogenic *Neisseria* are routinely found in sputum, *M catarrhalis* may be overlooked unless further microbiological evaluation is performed. In high-risk populations, *M catarrhalis* is a consistent finding in sputum cultures. For example, *M catarrhalis* was identified in 457 (2.7%) of all samples submitted for culture at a Veterans' Administration hospital over a 42-month period.[85] It was second only to *H influenzae* and more common than *S pneumoniae* when only isolates yielding one of these three in pure culture were compared.[85]

Clinical presentation. *M catarrhalis* tends to produce mild disease, with low-grade fever and patchy alveolar infiltrates.[84,85] Pleural effusions are rare. A clear seasonal variation exists, and most cases occur between October and April.[85,86] In a series of 42 cases,[86] most patients were older than 65 years and malnourished. Seventy-five percent had COPD.

Treatment. Beta-lactamase is produced by 60% to 75% of isolates.[86,87] The organism is sensitive to tetracycline, trimethoprim-sulfamethoxazole, third-generation cephalosporins, the new macrolides, quinolones, and a combination of amoxicillin and clavulanic acid.[84]

MANAGEMENT

The goals of the initial assessment are to determine a likely cause of the pneumonia and to assess its severity; both factors influence the need for hospitalization or intensive care.[11] Historical clues that often suggest a microbial differential diagnosis include comorbid illnesses, environmental exposures, relevant travel, and occupational and sexual histories.

TABLE 4
RISK FACTORS FOR MORTALITY IN COMMUNITY-ACQUIRED PNEUMONIA

Age > 65 years
Comorbid illness
Immunocompromised state
Neoplastic disease
Chronic lung disease
Diabetes mellitus
Chronic renal failure
Congestive heart failure
Chronic liver disease
Post splenectomy state
History of alcohol abuse or malnutrition
Physical examination findings
Abnormal vital signs
Respiratory rate > 30
Blood pressure < 90/60 mm Hg
Normal or low temperature
Altered mental status
Evidence of extrapulmonary site of infection
Laboratory findings
White blood cell count < 4 or > 30 $\times 10^9$/L
PaO_2 < 60 mm Hg or $PaCO_2$ > 50 mm Hg
Hemoglobin concentration < 9 g/dL
Need for mechanical ventilation
Blood urea nitrogen concentration > 20 mg/dL
Creatinine concentration > 1.2 mg/dL
Chest radiographic evidence of multilobe involvement
Other laboratory evidence of multiorgan dysfunction

When do patients need hospitalization?

Disease severity and risk of death guide the decision to hospitalize. *Table 4* outlines clinical features that were associated with mortality in multiple studies.[1] This information is readily available from the history, physical examination, and a few basic laboratory tests. Several investigators have attempted to define mortality risk on the basis of specific risk factors.[1,88] For example, Farr et al[88] found that the presence of two or more of the following predicted death with 70% sensitivity and 84% specificity: diastolic blood pressure ≤ 60 mm Hg, respiratory rate ≥ 30, and blood urea nitrogen (BUN) concentration ≥ 7 mmol/L.

Recently, Fine et al[89,90] developed a prognostic index based on six risk factors, and subsequently validated it both prospectively and retrospectively (*Table 5*). This index may prove useful in distin-

TABLE 5
MORTALITY RISK INDEX FOR PATIENTS WITH PNEUMONIA*

Finding	Points
Age > 65 years	+1
High-risk etiology *Staphylococcus aureus* Gram-negative pneumonia Aspiration pneumonia Post-obstructive pneumonia	+2
Vital sign abnormality	+2
Altered mental status	+2
Pleuritic chest pain	–2
Neoplastic disease	+4

Class	Points	Mortality rate (%)
I	< 0	0.1%
II	0	1.1%
III	1–4	8.6%
IV	5–7	26.2%
V	8–11	37.7%

*From Fine et al, references 88 and 89, with permission

guishing patients who can be safely cared for as outpatients from those requiring hospitalization, or possibly, intensive care. However, physician judgement remains the final arbiter. If there is doubt, the patient should be hospitalized until the clinical course has declared itself.

What tests are necessary?

What constitutes a cost-effective diagnostic evaluation depends on the severity of the clinical presentation. In relatively well outpatients, empiric therapy without further investigation is appropriate, but the optimal evaluation of patients requiring hospitalization is less well defined.

Gram's stains and cultures. Although the diagnostic value of sputum Gram's stains and cultures has been questioned, these tests are noninvasive and inexpensive compared with the cost of the hospitalization. A compelling sputum Gram's stain obtained before starting antibiotic therapy may be very helpful in selecting an initial antibiotic regimen. Therefore, a sputum Gram's stain should be obtained, if possible, in patients requiring hospital admission.

Sputum direct fluorescent antibody. A sputum DFA should be obtained in patients with suspected *Legionella* infections. Legionellosis may be indistinguishable from other types of CAP, but should be suspected in patients with many polymorphonuclear leukocytes but no organisms on sputum Gram's stain, in patients with hyponatremia, and in those with pneumonia that fails to respond to beta-lactam therapy. A pulse-temperature dissociation also suggests *Legionella*, as well as *Mycoplasma*, viruses, or *C pneumoniae*.

Sputum cultures. Sputum cultures must be interpreted in light of sputum Gram's stain results. Sputum samples with fewer than 10 squamous epithelial cells and more than 25 white blood cells per high-powered field provide more specific culture results,[91] but the sensitivity and specificity of sputum cultures remains low. A study comparing cultures of lung aspirates and sputum from 25 patients with CAP who had not yet received antibiotics found 20 potential pathogens in sputum cultures (including four cultures with pneumococci) that were not identified in the lung aspirate cultures.[92]

Other cultures. Blood cultures are positive in only 20% to 30% of CAP cases but provide specific, prognostically useful information. Pleural fluid should be aspirated both for diagnosis and to determine the need for chest-tube drainage. More invasive techniques such as fiberoptic bronchoscopy with bronchoalveolar lavage and protected specimen brushing have a higher diagnostic yield than sputum examination alone. The combined use of bronchoalveolar lavage and protected specimen brushing yielded a diagnosis in 32 (84%) of 40 patients with moderately severe CAP not previously treated with antibiotics in one study.[93] However, use of antibiotics significantly decreases the yield: in a separate study employing a variety of diagnostic methods in patients with severe CAP requiring intensive care, the bronchoscopic yield was only 34% (10 of 29) in patients receiving antibiotics.[94]

Routine microbiologic testing. The value of routine microbiologic testing in all patients with CAP has been questioned. In a study of 122 patients admitted to a teaching hospital and a district hospital, blood cultures were obtained in 81%, sputum cultures in 45%, and complete serologic testing in 28%.[95] No causative organism was identified in 74% of cases, and microbiologic results caused a change in antibiotic therapy in only 8%. In a similar study, the prognosis of 75 of 116 immunocompetent patients with CAP in whom an organism was identified was comparable to that in those without an identified organism.[96]

Recommendations. In summary, routine microbiologic testing is not warranted in otherwise-healthy outpatients with CAP who do not require hospitali-

TABLE 6
EMPIRIC ANTIBIOTIC CHOICES BY PATIENT SUBSET*

Patient profile	Likely organisms	Miscellaneous organisms	Therapy
Outpatients younger than 60 years without comorbidity	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* Viruses *Chlamydia pneumoniae* *Haemophilus influenzae*	*Legionella* species *Staphylococcus aureus* *Mycobacterium tuberculosis* Fungi Aerobic gram-negative bacilli	A macrolide† or tetracycline‡
Outpatients older than 60 years or with comorbidity	*S pneumoniae* Viruses *H influenzae* Aerobic gram-negative bacilli§ *S aureus*§	*Moraxella catarrhalis* *Legionella* species *M tuberculosis* Fungi	A second-generation cephalosporin or trimethoprim-sulfamethoxazole
Hospitalized patients	*S pneumoniae* *H influenzae* Multiple organisms Anaerobes Aerobic gram-negative bacilli *S aureus* *C pneumoniae* Viruses	*M pneumoniae* *M catarrhalis* *M tuberculosis* Fungi *C pneumoniae*	A macrolide† and either a beta-lactam/beta-lactamase inhibitor or a second- or third-generation cephalosporin
Severely ill hospitalized patients	*S pneumoniae* *Legionella* species Aerobic gram-negative bacilli *M pneumoniae* Viruses *S aureus*	*H influenzae* *M tuberculosis* Fungi	A macrolide and either a third-generation cephalosporin with antipseudomonal activity or another antipseudomonal agent such as imipenem-cilastatin, ciprofloxacin¶

*From the American Thoracic Society, reference 1; excludes patients at risk for HIV
†Erythromycin; the newer macrolides, clarithromycin and azithromycin, should be considered in those intolerant of erythromycin, and in smokers (to treat *H influenzae*)
‡Many isolates of *S pneumoniae* are resistant to tetracycline, and it should be used only if patient is allergic to or intolerant of macrolides
§In most cases, patients with these infections should be hospitalized for initial management; rifampin may be added if *Legionella* is documented
¶Although uncommon, because of high mortality associated with *Pseudomonas aeruginosa* pneumonia, a third-generation cephalosporin with antipseudomonal activity or other antipseudomonal agent such as imipenem-cilastatin and an aminoglycoside should be used for at least the first few days of treatment

zation. In an era of changing antimicrobial sensitivity patterns, we do favor obtaining sputum Gram's stains and cultures and blood cultures in patients requiring hospital admission, although further investigation may permit refinement of this recommendation.

Fiberoptic bronchoscopy should be reserved for severe cases of CAP or immunocompromised patients in whom an opportunistic infection is suspected. Ideally, the procedure should be performed before antibiotics are started; however, treatment should not be withheld if the procedure is not readily available.

Serologic testing is probably not indicated in most CAP patients treated as outpatients except to clarify epidemiologic trends. Serologic tests for IgM antibodies may provide early, clinically useful information in hospitalized patients. Similarly, a urine sample for *Legionella* antigen may provide helpful information in the appropriate clinical setting.

TREATMENT

Empiric therapy

The treatment of CAP is guided by the patient's age, concomitant illnesses, risk factors for specific infectious organisms, and illness severity. *Table* 6 is adapted from the American Thoracic Society position statement and lists likely pathogens and appropriate empiric antibiotic choices for each of the treatment groups.[1] Newer antibiotics are significantly more expensive than older ones.

For empiric therapy, erythromycin is the agent of choice in nonsmokers younger than age 60 without comorbid illness. The newer macrolides, azithromycin and clarithromycin, offer improved tolerance

and cover a broader spectrum of organisms (including *H influenzae*), but cost significantly more. Azithromycin's dosage schedule (once daily for 5 days) also offers a potential compliance advantage. Doxycycline is a reasonable choice if the patient cannot tolerate the macrolides, although many *S pneumoniae* isolates are resistant to tetracyclines.

Gram-negative organisms and *S aureus* are a greater concern in older patients and in those with concomitant illnesses. Initial hospitalization for intravenous antibiotic therapy should be strongly considered in this patient subset. Trimethoprim-sulfamethoxazole is an inexpensive, reasonable choice if *S aureus* is not a concern. Second-generation cephalosporins, the new macrolides, or a formulation of a beta-lactam combined with a beta-lactamase inhibitor provide good coverage of potential pathogens in less-ill patients.

Therapy in hospitalized patients

Antibiotic selection in patients sufficiently ill to require hospital care should be guided by the sputum Gram's stain, if available. Sputum and blood culture results available at 48 hours may permit directed antibiotic coverage. Empiric antibiotic choices should cover *S pneumoniae*, *H influenzae*, and atypical pathogens. A second- or third-generation cephalosporin or a beta-lactam–beta-lactamase inhibitor together with a macrolide provides appropriate coverage. If aspiration is suspected, penicillin or clindamycin is appropriate, unless the patient has been institutionalized or recently receiving antibiotics, in which case additional gram-negative coverage should be provided. Finally, antibiotic coverage for the critically ill patient should include antipseudomonal coverage plus erythromycin in adequate doses to cover for *Legionella* species (1 gram every 6 hours). The addition of rifampin should be considered if *Legionella* infection is documented and the patient is critically ill.

Duration of treatment

Ten days of therapy is appropriate for most cases. Because azithromycin has an exceedingly long tissue half-life, 5 days of azithromycin therapy appears comparable to 10 days of erythromycin therapy. Patients with suspected M *pneumoniae* pneumonia should receive erythromycin for 14 days. Otherwise-healthy patients with *Legionella* species should be treated with erythromycin for at least 14 days, but immunocompromised patients with *Legionella* species should receive 21 days of therapy. Similarly, many patients with C *pneumoniae* will require 14 to 21 days of therapy to fully clear the infection.

The clinical response to therapy varies with the patient's age and associated comorbid illnesses. Fever and leukocytosis usually resolve in 2 to 4 days. Abnormal findings on physical examination persist beyond 7 days in 20% to 40% of patients.[1] Persistence of fever after 4 days should raise the possibility of another pathogen that is not sensitive to the medications being used, an unrecognized closed-space infection such as an empyema, or a drug reaction if other clinical parameters are improving. Radiographic clearing occurs in less than 4 weeks in 80% to 90% of healthy patients younger than 50 years.[97] Conversely, in a recent study of 81 patients with CAP, radiographic clearing occurred by 1 month in only 30% of patients older than 50 or with underlying illnesses such as COPD and alcoholism.[97] Forty-one (50.6%) demonstrated complete clearance after 2 weeks and 50 (67%) of 75 by 4 weeks.[97] Clearance was faster in patients treated as outpatients (3.8 weeks vs 9.1 weeks), in nonsmokers (4.5 weeks vs 8.4 weeks), and in patients with single-lobe involvement. Other conditions associated with delayed clearing included diabetes mellitus and congestive heart failure.[97]

Obstructing lesions such as bronchogenic carcinoma are rare causes of delayed resolution, arguing against the need for early bronchoscopy.[97] The clinical response does not appear to predict the rate of radiographic resolution. More extensive radiographic involvement at presentation and deterioration after the start of therapy are predictive of slower radiographic resolution. *Legionella* infections may clear more slowly: only 50% cleared by 10 weeks in one study,[43] whereas M *pneumoniae* and C *pneumoniae* tend to clear more rapidly.[97]

In hospitalized patients, parenteral therapy should be continued until a clinical response is evident. This generally requires 3 to 7 days in immunocompetent patients, but longer in those with impaired immunity. Once fever has abated and patients have improved clinically, oral therapy can be used.

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