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Etiology of Community-Acquired Pneumonia

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Despite recent advances in diagnosis and treatment, community-acquired pneumonia (CAP) is still a common and potentially lethal infectious disease. CAP is the leading cause of death from infectious diseases and the sixth-ranked cause of death overall in the United States [1]. It is estimated that 4 to 5 million cases of CAP occur annually, accounting for approximately 10 million physician visits, 500,000 hospitalizations, 45,000 deaths, and an annual cost of $23 billion [2,3]. The overall CAP-related mortality rate has ranged from 2% to 30% among hospitalized patients, whereas the mortality rate is less than 1% for patients who are not hospitalized [2].

Disputes over diagnostic evaluations and therapeutic decisions exist for patients with CAP [1]. The causative pathogen remains unknown in 30% to 60% of cases despite vigorous clinical investigation [4]. Based on a review of more than 15 published reports from North America covering more than two decades of experience in hospitalized patients, the detection of specific bacterial pathogens as causes of pneumonia ranges from 20% to 60% for *Streptococcus pneumoniae,* 3% to 10% for *Haemophilus influenzae,* 1% to 6% for *Mycoplasma pneumoniae*, 4% for *Chlamydia pneumoniae*, 2% to 8% for *Legionella* species, 2% for viruses, 6% to 10% for aspiration, 3% for *Staphylococcus aureus*, 3% to 5% for gram-negative bacilli, and 10% to 20% for other identified causes [1]. This article summarizes the epidemiology, risk factors, and outcomes of microorganisms associated with CAP.

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Etiology of community-acquired pneumonia

At least six important host defense mechanisms are important in the prevention of CAP: aerodynamic filtration, the cough reflex, mucociliary transport, phagocytic cell function, immunologic function, and the clearance of pulmonary secretions. Deficiencies in normal host defense mechanisms influence the epidemiology, risk factors, and outcomes for CAP [5]. The etiology of CAP can be defined broadly into typical pathogens (eg, *S pneumoniae*, *H influenza*, and *Moraxella catarrhalis*), atypical pathogens (eg, *Legionella* spp, *M pneumoniae*, *C pneumoniae*), viruses, aspiration, and other agents. The etiologic agents and risk factors of common CAP pathogens for immunocompetent hosts are summarized in Table 1. In immunocompromised hosts, in addition to the usual pathogens, the etiology of CAP also includes opportunistic infections, such as *Mycobacterium tuberculosis*, *Pneumocystis jiroveci* pneumonia (PCP), and other opportunistic fungal infections (Table 2). Coexisting pulmonary pathogens should be considered when clinical isolates have been detected, when patients lack clinical improvement, and when patients have clinical deterioration despite seemingly appropriate treatment.

Typical pathogens

Streptococcus pneumoniae

Epidemiology

S pneumoniae is among the leading infectious causes of illness and death from CAP worldwide for young children, for persons who have underlying

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Table 1
Etiology of common community-acquired pneumonia pathogens in immunocompetent hosts

Etiology	Ambulatory setting	Hospitalization setting	Nursing home setting	ICU setting	Risk factors
Bacteria					
Streptococcus pneumoniae	5%–11%	5%–42.8%	6%–29.8%	11%–37.5%	Black race, smoking, seizure disorder, dementia, COPD, CHF, HIV
Haemophilus influenzae	2%–12%	1%–11%	2.5%–19%	—	COPD, prior antibiotic, oral steroid[a]
Staphylococcus aureus	—	1%–5%	1.7%–26%	3%–18%	Advanced age, prolonged hospitalization, prior antibiotic, several comorbidities
Gram-negative bacilli	—	0.7%–7%	5.3%–23%	3%–25%	Bronchiectasis, malignancy, CF, aplastic anemia
Moraxella catarrhalis	—	—	3.8%–5.5%	—	COPD, bronchiectasis, CHF, DM, malignancy, oral steroid
Atypical agents					
Legionella pneumophila	—	2%–6%	—	3%–22.8%	Renal and hepatic failure, DM, exposure[b], recent travel[c]
Mycoplasma pneumoniae	17.4%–37%	2%–32.5%	—	—	Contact with patient with similar symptoms
Chlamydia pneumoniae	5.3%–10.7%	5%–17.9%	6.6%	—	Advanced age, several comorbidities
Aspiration	—	—	14.5%	—	—
Unknown	41%–55%	—	13%–76.7%	25%–41.2%	—

Abbreviations: CF, cystic fibrosis; CHF, congestive heart failure; DM, diabetes mellitus.
[a] History of steroid use within the past 3 months.
[b] Exposure to hot tub and whirlpool-type spas, including recent repair with plumbing.
[c] Recent travel with an overnight stay outside the home.

chronic systemic conditions, and for the elderly. The pneumococcus had been identified in 5% to 11% of patients with CAP treated on an ambulatory basis, in 5% to 43% of patients with CAP who require hospitalization, and in 11% to 38% of patients with CAP who require admission to an intensive care unit (ICU) [4,6–9]. In a meta-analysis of 122 reports of CAP from 1966 through 1995, *S pneumoniae* accounted for the majority of over 7000 cases (66%) in which an etiologic diagnosis was made and for 66% of the lethal pneumonias [10]. In addition, the pneumococcus is the most common cause (60%) of bacteremic pneumonia [7].

Risk factors

Specific risk factors for pneumococcal infection include dementia, seizure disorders, congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), HIV, black race, overcrowding in institutions, and smoking [11–12]. In the United States, nonsusceptibility to penicillin has increased significantly during the past decade [13]. Frequently, rates of penicillin-resistant *S pneumoniae* (PRSP) are in excess of 30% [14]. The minimal inhibitory concentrations (MICs) for most strains with high-level resistance are 2 to 4 μg/mL. Of concern, the increasing rate of penicillin resistance is associated with resistance to beta-lactams and other classes of antibiotics, such as macrolides, tetracycline, and trimethoprim-sulfamethoxazole [14]. With the increase in the rate of PRSP, physicians should be aware of the changing epidemiology and microbiology of pneumococcal disease to provide appropriate empiric antimicrobial treatment.

Haemophilus influenzae

Epidemiology

Haemophilus influenzae, a fastidious gram-negative coccobacillus bacteria, is the third most common cause of CAP identified in patients who require hospitalization [6]. *H influenzae* accounts for 2% to 12% of CAP in patients treated on an ambulatory basis, 1% to 11% of CAP in patients who require hospitalization, and 3% to 19% of pneumonic cases in nursing home residents [4,6–9]. Most *H influenzae* clinical isolates are nontypeable stains recovered

Table 2
Etiology of common community-acquired pneumonia in HIV-infected patients

Etiology	Area of endemicity	Incidence	Risk factors
Bacterial	Ubiquitous	1.9–19.2 cases/100 patient-years	Decreasing CD4 cell counts, injection drug use, prior sinusitis and respiratory tract infection, use of TMP-SMX[d]
Mycobacterial	Ubiquitous	1.4–16.2 cases/100 patient-years	Injection drug use, homeless, PPD skin test positive
Opportunistic fungal infections			
Pneumocystis jeroveci	Ubiquitous	0.22–4.6 cases/100 patient-years	CD4 <200 cells/mm^3, clinical marker[e], the occurrence of previous pneumonia and AIDS-defining illness
Cryptococcus neoformans	Ubiquitous	ND	CD4 <100 cells/mm^3, black race, injection drug use, cigarette smoking
Histoplasma capsulatum	North American river valleys, Europe, Africa, Southeast Asia, Caribbean, Central and South America Argentina, Central America	1%–25%[a]	Age, underlying immunosuppression
Coccidioides immitis	Southwestern United States, Northwestern Mexico	0.3%–8.2%[b]	CD4 <250 cells/mm^3, clinical diagnosis of AIDS
Penicillium marnefeii	Southern China, Hong Kong, Thailand, Vietnam	15%–20%[c]	Exposure to environmental reservoirs[f]

Abbreviations: ND, no data; PPD, purified protein derivative; TMP-SMX, trimethoprim-sulfamethoxazole.
[a] Incidence varies from <1% of patients in nonendemic areas to 25% of patients in endemic areas.
[b] Incidence varies from 0.3% nationwide (United States) to 8.2% in Arizona.
[c] Accounting for 15% to 20% of all AIDS-related illness in Northern Thailand.
[d] This factor was found to be protective.
[e] Including wasting syndrome, the occurrence of a previous episode of pneumonia of any type, or the occurrence of previous AIDS-defining events.
[f] Occupational or other exposure to soil in Northern Thailand.

from patients during the winter months [3]. In a meta-analysis of 33,148 patients from 127 studies, *H influenzae* was the cause in 844 (3%) patients [10].

Risk factors

Most studies have shown a higher prevalence of *H influenza* pneumonia among patients with COPD [15]. Other risk factors include the use of antibiotics or oral steroids within the past 3 months [6]. Currently, more than 30% of *H influenzae* isolates in Canada have aminopenicillin resistance owing to β-lactamase production [16]. Nearly all strains are susceptible to ceftriaxone and cefuroxime, yet more than 50% of β-lactamase–producing *H influenza* isolates display either intermediate or high-level or resistance to clarithromycin [17].

Moraxella catarrhalis

Epidemiology

Approximately 1% to 5% of healthy adults are colonized by *M catarrhalis* [18,19]. Adults with chronic lung disease have been reported to have higher rates of *M catarrhalis* respiratory tract colonization when compared with healthy adults [18]. A study of adult carrier rates of *M catarrhalis* showed differential rates by age, that is, 5% versus 27% for adults aged less and more than 60 years, respectively [19]. Three separate but related clinical scenarios have been defined for *M catarrhalis* lower respiratory tract infections: (1) infection causing a COPD exacerbation, (2) infection causing pneumonia, especially in an older adult, and (3) infection as a nosocomial respiratory tract pathogen [18]. *M catarrhalis* pneumonia occurs predominantly in the winter months and is responsible for 4% to 6% of nursing home–acquired pneumonia and 10% of CAP in the elderly [3,19].

Risk factors

Most elderly patients who experience pneumonia owing to *M catarrhalis* have underlying cardiopulmonary disease, including COPD, bronchiectasis, congestive heart failure, or predisposition to aspira-

tion [20]. Other predisposing conditions associated with *M catarrhalis* infection include corticosteroid therapy, diabetes mellitus and malignancies [18]. Although *M catarrhalis* pneumonia causes a significant illness in elderly patients, fulminant pneumonia, pleural effusion, and empyema are uncommon [18]. Most (90%) strains of *M catarrhalis* produce an inducible β-lactamase [21]. The β-lactamase is more active against penicillins than cephalosporins, and its activity is inhibited by β-lactamase inhibitors. These strains show an inoculum-dependent susceptibility to ampicillin; therefore, ampicillin should not be used for these strains regardless of the results of susceptibility testing.

Staphylococcus aureus

Epidemiology

Pneumonia owing to *S aureus* accounts for 1% to 5% of patients with CAP who require hospitalization and 2% to 26% of patients with nursing home–acquired pneumonia [4,6–9]. Clinical manifestations are similar to those with CAP from other bacterial etiologies [22,23], although the mortality may be higher [23,24]. Radiologic patterns are protean, inclusive of cavity formations [23,25]. Methicillin-resistant *S aureus* (MRSA) remains more of a concern for hospital-acquired pneumonia (HAP), although it has been reported as a cause in CAP [23,24].

Risk factors

The risk factors associated with *S aureus* pneumonia include advanced age, prolonged hospitalization, underlying lung disease, prior antibiotic therapy, and surgery or other invasive procedures [22,24]. MRSA pneumonia tends to produce a significantly greater frequency of bacteremia and septic shock and may associated with higher mortality [22].

Aerobic gram-negative pneumonia

Epidemiology

Aerobic gram-negative pneumonia accounts for 1% to 7% of patients with CAP who require hospitalization and 5% to 23% of HAP and nursing home–acquired pneumonia [4,6–9]. These pathogens also have been identified in severe CAP; although rare, such cases often are rapidly progressive and may be fatal [26].

Risk factors

Aerobic gram-negative pneumonia, especially with *Pseudomonas aeruginosa*, is a prognostic indicator of mortality in patients with CAP. Most cases occur in patients with underlying diseases, such as malignancy, cystic fibrosis, aplastic anemia, and bronchiectasis [9]. Environmental exposure to dusts containing metals such as iron have been associated with *Acinetobacter* CAP, whereas exposure to water aerosolization has been associated with *P aeruginosa* pneumonia [26].

Anaerobic bacterial pneumonia

Epidemiology

The frequency of anaerobic infection among patients with CAP is not known, because the methods required to obtain valid uncontaminated specimens for meaningful anaerobic culture have rarely been used. Nonetheless, anaerobic bacteria are the most common etiologic agents of lung abscess and aspiration pneumonia, and these bacteria are relatively common isolates from empyemas [3,27]. Patients with anaerobic bacterial infection may also present with pneumonitis that is indistinguishable from other forms of bacterial pneumonia [28].

Risk factors

Factors that predispose to anaerobic bacterial pneumonia include aspiration, infection of the gingival crevice (gingivitis), necrosis of tissue with abscess formation or bronchopulmonary fistula, infection complicating airway obstruction, and infection in a dependent pulmonary segment [27]. Some studies have suggested that anaerobes may account for a substantial number of cases of CAP that have these characteristic features [29].

Atypical pathogens

Mycoplasma pneumoniae

Epidemiology

M pneumoniae is a common cause of respiratory tract infection in young adults, attributable for 17% to 37% of outpatient CAP and 2% to 33% of patients with CAP who require hospitalization [5–9]. After an incubation period of 2 to 4 weeks, approximately 3% of patients have clinical and radiographic evidence of pneumonia. Common symptoms include a prodromal period with fever, chills, headache, and sore throat followed by a dry nocturnal or productive cough of mucoid sputum that persists for 3 to 4 weeks [3]. Extrapulmonary manifestations may include hemolytic anemia, nausea and vomiting, myocarditis, rash, and diverse neurologic syndromes.

Risk factors

A possible clue to help diagnose *M pneumoniae* pneumonia is a history of contact with a person with a similar condition characterized by a long incubation period. Currently, there is no reliable diagnostic test to detect *M pneumoniae* infection; therefore, macrolide or tetracycline-based therapy usually is empirical.

Chlamydia pneumoniae

Epidemiology

The prevalence of pneumonia owing to *C pneumoniae* varies from year to year and within geographic settings. Studies indicate that *C pneumoniae* is linked to 5% to 11% of patients with CAP who are treated on an ambulatory basis, 5% to 18% of patients with CAP who require hospitalization, and approximately 7% of patients with nursing home–acquired pneumonia [5–9]. The clinical spectrum ranges from asymptomatic infection to life-threatening pneumonia. When seen in CAP as one of two pathogens, the associated pathogen seems to influence the clinical course and outcome [30].

Risk factors

In *C pneumoniae* pneumonia, sore throat, hoarseness, and headache are important nonpneumonic symptoms; other findings include sinusitis, reactive airway disease, and empyema [3]. Advanced age and several comorbidities are risk factors for hospitalization in patients with pneumonia owing to *C pneumoniae* [3]. The preferred diagnostic test is an assay of acute and convalescent specimens to detect a fourfold increase in antibody titers, with supporting evidence based on throat swab polymerase chain reaction or culture results [3,31]. Nevertheless, with the limitation and availability of diagnostic tests, treatment most often is empirical.

Legionella pneumophila *and other* Legionella *species*

Epidemiology

Legionella species are implicated in 2% to 6% of patients with CAP who require hospitalization [7–8]. Although rare in immunocompetent adults younger than 30 years of age, legionellosis can be a major cause of lethal pneumonia, with mortality rates of 5% to 25% among immunocompetent hosts and substantially higher rates among immunosuppressed hosts [32]. Clinical features of Legionnaires' disease include high fever, hyponatremia, central nervous system manifestations, elevated lactate dehydrogenase levels, and the presence of severe disease [32].

Risk factors

Epidemiologic risk factors for Legionnaires' disease include recent travel with an overnight stay outside the home, recent repair of domestic plumbing, exposure to hot tub and whirlpool-type spas, renal or hepatic failure, diabetes, or systemic malignancy [33,34]. In addition, increasing age, smoking, and compromised cell-mediated immunity are associated with Legionnaires' disease [33]. Diagnostic tests for Legionnaires' disease include the urine antigen assay for *L pneumophila* serogroup 1 and culture on selective media, which detects all *Legionella* strains but is technically demanding [3].

Miscellaneous causes of community-acquired pneumonia

A wide variety of pathogens, such as *M tuberculosis*, fungi, viruses, nocardia, *Chlamydia psittaci*, Hantavirus, *Coxiella burnettii*, *P jiroveci*, *Leptospira*, and uncommon pathogens such as tularemia may be responsible for CAP, depending on the patient's host defense system and exposures. Physicians should consider epidemiologic risk factors in the diagnosis and treatment of CAP, especially in patients who do not respond to a standard therapeutic regimen for CAP (Table 3).

Community-acquired pneumonia and HIV/AIDS

Immunocompromised patients, especially those with HIV infection, have increased risk for routine and unusual CAP pathogens. The etiology of CAP in immunocompromised patients, with a focus on hosts with HIV infection, has been summarized previously in Table 2. The etiology and epidemiology of CAP in cancer and transplant patients is addressed elsewhere in this issue.

Bacterial pneumonia

Bacterial pneumonia continues to be an important problem in patients with HIV infection. Pneumonia remains the chief cause of hospitalization for patients with HIV/AIDS, even in the era of combination antiretroviral therapy (ART) [35]. The incidence of bacterial pneumonia in HIV patients ranges from 2 to 19 cases per 100 patients/year [36–38]. Low CD4 cell counts, injection drug use, prior sinusitis, and

Table 3
Epidemiology and etiology of community-acquired pneumonia based on medical history

Medical history	Possible etiology
Host	
Alcoholism	*S pneumoniae*, anaerobes, aerobic gram-negative rods
COPD/smoker	*S pneumoniae*, *H influenzae*, *M catarrhalis*, *L pneumophilia*
Poor dental hygiene	Anaerobes
HIV infection (early stage)	*S pneumoniae*, *H influenzae*, *M tuberculosis*
HIV infection (CD4 cell counts < 200/μL)	*P jiroveci*, *S pneumoniae*, *H influenzae*, *C neoformans*, *M tuberculosis*
Granulocytopenia	Aerobic gram-negative rods
Environmental	
Increased terrorist activity	*B anthracis*, *Y pestis*, *F tularensis*
Exposure to contaminated air-conditioning cooling towers; hot tubs; recent travel and stay in a hotel; grocery store mist machine; visit to or recent stay in a hospital with drinking water contaminated by *Legionella pneumophilia*	*L pneumophilia*
Exposure to infected parturient cats, cattle, sheep, or goats	*C burnetti*
Pneumonia develops after windstorm in an area of endemicity	*C immitis*
Outbreak of pneumonia in shelter for homeless men or jail	*S pneumoniae*, *M tuberculosis*
Outbreak of pneumonia in military training camp	*S pneumoniae*, *C pneumoniae*, adenovirus, *M pneumoniae*
Outbreak of pneumonia in a nursing home	*C pneumoniae*, *S pneumoniae*, RSV, influenza A virus
Exposure to contaminated bat caves; excavation in areas of endemicity	*H capsulatum*
Exposure to turkeys, chickens, ducks, or psittacine birds	*C psittaci*, avian influenza[a]
Exposure to mice or mice droppings	Hantavirus
Exposure to rabits	*F tularencis*
Travel history	
Travel to Thailand or other countries in Southeast Asia	*B pseudomaleii* (melioidosis)
Immigration from countries with high endemic prevalence of tuberculosis	*M tuberculosis*
Travel to endemic areas of SARS[a]	SARS-corona virus
Occupational history	
Health care worker	*M tuberculosis*, acute HIV seroconversion with pneumonia
Tick bite	Rocky Mountain spotted fever, *Ehrlichia* species

[a] Endemic areas of these agents may change from year to year. Physicians should consult www.cdc.gov, www.who.int periodically.

Adapted from Mandell LA, Marrie TJ, Grossman RF, et al. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. Clin Infect Dis 2000;31:383–421; with permission.

prior lower respiratory tract bacterial infection are risk factors for bacterial pneumonia in patients with HIV infection [38,39], whereas trimethoprim-sulfamethoxazole prophylaxis is associated with a lower risk of bacterial pneumonia [38,40,41]. Several studies have confirmed bacterial pneumonia to be the most common pulmonary complication in patients with HIV/AIDS. *S pneumoniae*, *S aureus, H influenzae,* and *M pneumoniae* are the most frequent pathogens identified [5,38,42,43]. In addition, there is a trend toward higher mortality and more frequent presentation of severe pneumonia caused by *P aeruginosa*, especially in patients with advanced HIV/AIDS [36,44].

Mycobacterial pneumonia

Among the types of mycobacterial infections associated with HIV/AIDS, *M tuberculosis* is considered the most prevalent and important problem worldwide. The incidence of tuberculosis ranges from 1.4 to 2.2 cases per 100 person-years to 7.7 to 16.2 cases per 100 person-years, depending on the geographic location, prevalence rates of tuberculin test reactivity, and the demographic characteristics of the population [45,46]. It is estimated that 6000 to 9000 new cases of tuberculosis occur annually in the United States in patients with HIV/AIDS [45,47]. HIV-infected patients have markedly increased risks

for primary infection, reactivation of tuberculosis, and second episodes of tuberculosis from exogenous reinfection [47]. Most cases present as pulmonary infections, with case rates extraordinarily high among indigent patients and users of illicit drugs [47]. Clinical studies have shown the detrimental effects of tuberculosis on the course of HIV infection, with a twofold higher mortality in dual-infected hosts when compared with HIV-infected patients without tuberculosis, independent of CD4 cell count [47]. The degree of immunosuppression is the most important predictor of survival in HIV-infected patients with tuberculosis [48].

Notable nontuberculous mycobacterial infections in HIV-infected patients occur from *M kansasii*, *M scrofulaceum*, *M terrae*, *M gordonae*, *M chelonae, M genavence, M xenopi*, and *M fortuitum*. Although rare, isolated pulmonary *M avium complex* (MAC) infection has been reported in 20 patients with HIV infection [49].

Fungal pneumonia

With the advent of combination ART, the incidence of opportunistic infections in hosts with HIV infection has substantially declined [50]. Likewise, the incidence of opportunistic fungal infections is approximately 20% to 25% of the incidence seen in the mid-1990s. Despite the decline in the incidence of opportunistic infections, fungal infections are still common in patients with advanced HIV disease. Such infections occur in patients who are long-term nonpresenters, who are nonadherent to ART, or who do not seek medical care [50,51]. *P jiroveci* pneumonia (PCP) remains the most common opportunistic infection, whereas the incidence of pneumonia owing to *Cryptococcus neoformans*, *Histoplasma capsulatum, Coccidioides immitis*, and *Penicillium marneffei* varies greatly depending on the geographic location (see Table 2) [50,51]. As is true for tuberculous and nontuberculous mycobacterial infections, some cases of fungal pneumonias have been associated with the use of ART and the subsequent immune restoration from AIDS [51]. Because this syndrome may mask the clinical presentation of typical and atypical pneumonic infections, a high index of suspicion is necessary for early diagnosis.

Miscellaneous community-acquired pneumonia pathogens in HIV/AIDS

Infections from cytomegalovirus, herpes simplex virus, respiratory syncytial virus, and influenza virus readily occur in patients with HIV/AIDS. The true incidence and prevalence of these pathogens as causes of CAP in HIV-infected patients are unknown. In severely immunosuppressed hosts with PCP, coexisting pulmonary infection has been reported in as many as 40% of cases [52,53].

Special considerations

In recent years, newer agents such as Hantavirus, severe acute respiratory syndrome (SARS), and avian influenza have been identified as causes of CAP. Although rare, an isolated case or outbreak from agents of bioterrorism is plausible (www.who.int and www.cdc.gov). Pneumonic presentations of bioterrorist activity are likely attributed to *Bacillus anthracis*, *Yersinia pestis*, or *Francisella tularensis.* Any suspected case should be treated as an epidemiologic emergency. The local health department should be notified. Because these agents may be transmittable from person to person, a high index of suspicion will lead to prompt diagnosis and proper treatment. Initial assessment of all patients with CAP should include a travel history, animal exposures, and occupational risk (see Table 3).

Summary

The growing list of etiologic agents associated with CAP and the growing number of the at-risk population continue to challenge existing diagnostic modalities for this lower respiratory tract infection. Physicians should be aware of unusual presentations of common causes of CAP as well as common presentations of unusual causes of CAP. Empiric treatment remains the norm in patients with CAP.

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