Atypical Pneumonia: Definition, Causes, and Imaging Features

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Abbreviations: ARDS = acute respiratory distress syndrome, ATS = American Thoracic Society, CAP = community-acquired pneumonia, COVID-19 = coronavirus disease 2019, HMPV = human metapneumovirus, MERS = Middle East respiratory syndrome, MERS-CoV = Middle East respiratory syndrome coronavirus, PA = posteroanterior, RSV = respiratory syncytial virus, SARS = severe acute respiratory syndrome, SARS-CoV-1 = severe acute respiratory syndrome coronavirus 1, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Review the definition of the term *atypical pneumonia*.
- Define the classification of respiratory pathogens that are considered atypical.
- Discuss the role of imaging in the diagnosis of infections with atypical respiratory pathogens.

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Pneumonia is among the most common causes of death worldwide. The epidemiologic and clinical heterogeneity of pneumonia results in challenges in diagnosis and treatment. There is inconsistency in the definition of the group of microorganisms that cause "atypical pneumonia." Nevertheless, the use of this term in the medical and radiologic literature is common. Among the causes of community-acquired pneumonia, atypical bacteria are responsible for approximately 15% of cases. Zoonotic and nonzoonotic bacteria, as well as viruses, have been considered among the causes of atypical pneumonia in a patient who is immunocompetent and have been associated with major community outbreaks of respiratory infection, with relevant implications in public health policies. Considering the difficulty of isolating atypical microorganisms and the significant overlap in clinical manifestations, a targeted empirical therapy is not possible. Imaging plays an important role in the diagnosis and management of atypical pneumonia, as in many cases its findings may first suggest the possibility of an atypical infection. Clarifying and unifying the definition of atypical pneumonia among the medical community, including radiologists, are of extreme importance. The prompt diagnosis and prevention of community spread of some atypical microorganisms can have a relevant impact on local, regional, and global health policies.

Introduction

Despite the availability of antimicrobial agents and effective vaccines, pneumonia continues to be the leading cause of death worldwide and is among the most common causes of death and morbidity in the United States (1,2). Pneumonia is a heterogeneous illness both clinically and epidemiologically. This creates a challenge in the diagnosis, treatment, and follow-up of patients. Once suspected, the diagnosis and management of pneumonia are defined by the patient's risk factors (age, comorbidities, immunologic status, environmental exposures), physical examination findings, and the results of laboratory tests.

Pneumonia is classified into three subgroups on the basis of the clinical context in which the patient develops symptoms of infection: community-acquired pneumonia (CAP), hospital-acquired pneumonia, and ventilator-associated pneumonia. The use of the term *health care–associated pneumonia* was discontinued in the latest management guidelines (1,3).

CAP is defined as a lower respiratory tract infection acquired by a patient in a nonhospitalized setting, which is associated with clinical symptoms of acute infection and new opacities depicted on a chest radiograph, if one is obtained (4,5). The diagnosis of CAP is commonly based on clinical and laboratory findings; a large majority of patients receive empirical antibiotic treatment on an ambulatory basis (6). The role of imaging in the initial diagnosis of pneumonia

TEACHING POINTS

- The microorganisms included in the atypical pneumonia group are characterized by constitutional symptoms and upper and lower respiratory tract involvement and can have a protracted clinical course with gradual resolution. The lack of typical findings of lobar consolidation on chest radiographs, failure to isolate a pathogen with use of routine bacteriologic testing methods, and lack of response to penicillin therapy are also common features of this group of microorganisms.
- Infections with *M pneumoniae, C pneumoniae,* and *Legionella pneumoniae* are the most common nonzoonotic causes of atypical bacterial pneumonias.
- The most common zoonotic bacteria that cause pneumonias, *C psittaci, F tularensis,* and *C burnetii,* are important causes of CAP in specific immunocompetent populations.
- Respiratory viruses that most commonly affect humans include adenovirus, influenza A and B viruses, parainfluenza virus, RSV, human metapneumovirus, and coronaviruses.
- Chest radiography is the first imaging modality indicated in the diagnostic imaging workup of respiratory infections and, with minimal variability, is considered usually appropriate as the initial diagnostic test in the various scenarios of CAP. The role of chest CT in the diagnosis of CAP is limited to specific clinical scenarios and does not precede chest radiography in any case.

is controversial. Although the consensus guidelines from the Infectious Diseases Society of America and the American Thoracic Society (ATS) state that "a demonstrable infiltrate by chest radiograph or other imaging technique... is required for the diagnosis of pneumonia" (7), the sensitivity of chest radiography for the detection of pulmonary infiltrates is variable (8,9). Some consensus statements suggest that chest radiography be performed in all patients with suspected CAP, but other statements are not so definitive and support its use in specific patient populations, acknowledging that the management of pneumonia with empirical therapy based solely on clinical symptoms and laboratory test results is acceptable (6,10,11).

Microorganisms such as *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus* have been identified as common causes of CAP and are known as "typical" microorganisms in the cause of CAP (3). An evidence-based approach to the epidemiology of pneumonia is complex, and the exact etiologic microorganism remains unknown in almost 60% of cases (3,6). The microbiologic cause of pneumonia has changed over the years with the widespread use of the pneumococcal conjugate vaccine and the appearance of multidrug resistant pathogens. Other microorganisms including *Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella* species are currently considered common causes of CAP (3). The increased capacity to recognize other microorganisms such as viruses, which commonly coinfect patients with bacterial respiratory infections (12), also introduces variables and challenges in the current management of pneumonia.

Although controversial, currently the broad term *atypical pneumonia* is considered among the causes of CAP in patients who are immunocompetent. However, there is inconsistent information regarding the specific microorganisms considered in this group (7,13,14). The 2001 version of the guidelines for the management of adults with CAP by the ATS retains the term *atypical pneumonia* to specifically refer to the diagnosis and management of infection with three pathogens: *C pneumoniae, M pneumonia,* and *Legionella* spp (10). The guidelines reserve the use of this term to refer to the etiologic microorganism and not to the clinical presentation. A subsequent unified and updated guideline for the management of CAP from the Infectious Diseases Society of America and the ATS retains the term *atypical pneumonia* as well, although it includes viruses among the etiologic agents (7). Only the Japanese guidelines for the management of CAP consider atypical pneumonias in their treatment algorithm, although the microorganisms considered in this group (*C pneumoniae, M pneumoniae,* and *Coxiella burnetii*) differ from those defined by the ATS, likely on the basis of epidemiologic differences among communities and the low prevalence of *Legionella* spp in Japan (13,15). The Canadian guidelines for the management of CAP do not use the term *atypical pneumonia* but instead consider *M pneumoniae, C pneumoniae,* and *Legionella* spp as common causes of pneumonia in the ambulatory and inpatient settings (6).

Zoonotic atypical bacterial pneumonias (*Chlamydia psittaci, Francisella tularensis,* and *C burnetii*) are important causes of CAP in endemic areas and require a specific contact history of the patient with the animal vector (16). Although British, Canadian, Japanese, and American guidelines for the management of CAP consider some of these zoonotic microorganisms among the causes of severe pneumonia, none of these are included in the current management guidelines for CAP, among the atypical microorganisms (6,7,13,17). Similarly, viruses are also inconsistently considered among the causes of atypical pneumonia by some authors. Viruses are not consistently taken into account in management guidelines, despite being among the most frequent causes of respiratory infection in the community and responsible for a large number of outbreaks and pandemics of respiratory infection around the world (13,15,16,18,19).

The variable definition of *atypical pneumonia* in the medical literature, including the microorganisms that are considered within this group, has

also led to inconsistent use of this term in the radiologic literature and among radiologists. The term *primary atypical pneumonia* was originally used in the radiologic literature to describe the unusual imaging presentation of a pulmonary infection (20), although the use of the term has expanded in the radiologic jargon. The use of the term *atypical pneumonia* is frequently found in radiologic reports to reference the unknown cause of pulmonary opacities or the possibility of infection by fungi or viruses or other infections such as tuberculosis. Further, *atypical pneumonia* is a term commonly used in patients who are immunocompetent or immunosuppressed. Introducing this terminology into radiologic reports without clarity or agreement on what it entails yields low diagnostic value and a questionable contribution of imaging to the diagnosis and management of these infections.

Although excellent review articles of the clinical and imaging manifestations of specific microorganisms causing atypical pneumonia (as defined by the ATS) are available in multiple journals across specialties, the topic as a whole has not been revisited in the radiologic literature in the past 20 years or longer. Considering the progress in diagnostic tests, the increased knowledge about pathogens, and the advances in the understanding of the imaging evolution of diseases since the term *atypical pneumonia* was introduced to the medical literature in the 1930s, we consider it appropriate to revisit this topic.

In this article, we review the history and definition of the term *atypical pneumonia*, provide a comprehensive update of the most common microorganisms that belong to this group, and identify the main clinical and imaging features that characterize these infections. In addition, we review the impact of the infection by atypical microorganisms on public health and specific considerations in the imaging diagnosis and follow-up of these entities. Considering the number of variables that play a role in the diagnosis and management of pneumonia, this article exclusively reviews pulmonary infections in patients who are immunocompetent. Although atypical microorganisms can be the cause of pneumonia in both immunocompetent and immunosuppressed populations, we will not review the incidence, epidemiology, and complex management of pneumonia in patients who are immunocompromised in this article.

What Does *Atypical Pneumonia* Mean?

The term *atypical pneumonia* was introduced many decades ago in the medical literature to describe unusual clinical presentations of pulmonary infections for which a specific causative organism was not recognized. Despite many reports in the 1920s describing the unusual presentation of pulmonary infections in different patient populations, the term *atypical pneumonia* was popularized by Dr Hobart Reimann's publication in the *Journal of the American Medical Association* in 1938 (21). Initially used to describe pneumonias that differ clinically from ordinary manifestations, the term was later better defined in the 1940s as a distinct clinical entity characterized by gradual onset of constitutional and respiratory symptoms associated with an unusual radiographic pattern of pulmonary infection (22). At a time when the causes of bacterial pneumonia extended little beyond the classic pneumococcus (*S pneumoniae*) and tuberculosis (*Mycobacterium tuberculosis*) and diagnostic methods were limited, cases of atypical pneumonia were thought to be caused by an unidentified virus. Atypical pneumonia was the subject of research during World War II, described among military personnel in the United States and other regions of the world as an important cause of outbreaks and infections in new recruits as well as a wide variety of patient populations, including children (23). The presence of extrapulmonary symptoms and the resistance to conventional empirical antibiotic treatment (β-lactam) for pneumonia were described as common factors among the cases reported (3,4).

Atypical pneumonia as a term in the radiologic literature arrived also in the 1940s, with reports describing variable radiographic patterns in patients with respiratory illness of unknown cause (24). The description of multiple cases of respiratory infection termed *primary atypical pneumonia of unknown etiology* in 1943 (24) led to the recognition of unusual radiographic manifestations that differed from the more commonly observed radiographic pattern of lobar pneumonia, observed in multiple patients presenting with similar clinical symptoms. Although at the time most of these cases were deemed of unknown cause, most of them were likely caused by *M pneumoniae* (25). Although the term in the radiologic literature was introduced to describe the unusual imaging patterns observed in these cases, in the most recent update of the ATS guidelines, the term *atypical pneumonia* refers to the group of organisms causing the infection rather than the clinical or radiologic presentation (10). Some syndromic associations that characterize infection by specific causative microorganisms of atypical pneumonia have been described and proposed to be helpful in the initial diagnostic approach of pulmonary infections (16). However, there is considerable overlap among the clinical manifestations of both typical bacterial and atypical microorganisms. The diagnosis of an atypical pneumonia solely on the basis

of clinical presentation does not permit targeted therapeutic decisions to be made.

Despite the controversial use of the term *atypical pneumonia*, it continues to appear in the medical literature. The microorganisms included in the atypical pneumonia group are characterized by constitutional symptoms and upper and lower respiratory tract involvement and can have a protracted clinical course with gradual resolution. The lack of typical findings of lobar consolidation on chest radiographs, failure to isolate a pathogen with use of routine bacteriologic testing methods, and lack of response to penicillin therapy are also common features of this group of microorganisms (26). However, many of these pathogens may have varied imaging appearances, and some can present with lobar consolidation, indistinguishable from typical microorganisms causative of CAP.

One of the most relevant considerations when recognizing a lower respiratory infection as a possible atypical pneumonia is the impact on public health and health policies that these microorganisms may have. Historically, many "atypical" microorganisms have been responsible for severe CAP. Many of these microorganisms have also been implicated in outbreaks of respiratory infections in specific communities as well as in the general population. Viruses specifically have been responsible for the largest community outbreaks and global pandemics, such as the influenza pandemic in 2009 and the recent coronavirus disease 2019 (COVID-19) pandemic (27,28). Thus, the suspicion, early diagnosis, establishment of public health safety measures, and appropriate treatment of these atypical microorganisms are significantly relevant at a larger scale.

It is the authors' opinion that the use of the term *atypical pneumonia* in the radiologic report does hold value when referring to the suspicion for a specific group of microorganisms that require unique considerations for both diagnosis and management, as well as potential respiratory isolation and institution of safety health policies to the public. It is important to recognize that the microorganisms considered in the group of atypical bacterial nonzoonotic pneumonias as well as respiratory viruses are common causes of CAP in the general population; thus the term *atypical* does not equate to unusual or uncommon (29). For radiologists, the clinical information is not always readily available. However, the presence of an atypical radiologic pattern of pneumonia, in conjunction with clinical and epidemiologic data that differ from the ordinary or hint to specific environmental risk factors, should raise the suspicion for infection by an atypical microorganism.

The use of the term *atypical pneumonia* in the radiologic report, in our opinion, can be optimized by providing further guidance to the ordering clinician, specifically by stating if the radiographic pattern observed is commonly seen with typical infections or raises the possibility of alternative diagnosis and what those specific entities would be. The use of standardized reporting to convey the findings at chest radiography and CT in patients with suspected or proven COVID-19 in the recent pandemic is an excellent example of an attempt to provide clarity and guidance to lead management, despite the lack of pathognomonic imaging findings (30,31).

Atypical Bacterial and Viral Pneumonias

The atypical bacterial pneumonias that cause infection in patients who are immunocompetent represent approximately 15% of all CAPs. Although there are many clinical factors differentiating typical from atypical bacterial CAPs, the most important differentiating feature is the pattern of extrapulmonary involvement and systemic involvement that occurs in atypical bacterial pneumonias (16).

As a group, atypical pneumonias are classified clinically by the mode of transmission into nonzoonotic and zoonotic pneumonias. Infections with *M pneumoniae*, *C pneumoniae*, and *Legionella pneumoniae* are the most common nonzoonotic causes of atypical bacterial pneumonias (16,26). Nonzoonotic microorganisms coinfect a larger and uncertain percentage of patients with CAP, considering the difficulty in isolating these pathogens. Zoonotic pneumonias are less commonly seen in the general population and are specifically linked to unique environmental risk factors and the exposure to specific animal vectors. The most common zoonotic bacteria that cause pneumonias, *C psittaci*, *F tularensis*, and *C burnetii*, are important causes of CAP in specific immunocompetent populations.

Viral pneumonias are a wide group of infections caused by microorganisms responsible for common upper and lower respiratory tract infections. The true proportion of viral infection as an isolated cause of CAP is probably underestimated owing to limited testing and negative test results from nasopharyngeal and oropharyngeal swab polymerase chain reaction (PCR) tests, although a major meta-analysis reports an incidence of viral infection as a cause of pneumonia as high as 44% in the general population (28). Viruses can be consistently considered among the group of atypical pneumonias when accounting for their clinical, epidemiologic, and unique management characteristics. Influenza virus, parainfluenza virus, respiratory syncytial virus (RSV), adenovirus, and human metapneumovirus (HMPV) are

Table 1: Nonzoonotic Atypical Bacterial Pneumonias

Entity (Pathogen)	Transmission	Populations at Risk	Associated Clinical Findings	Laboratory Findings
Mycoplasma pneumonia or walking pneumonia *(M pneumoniae)*	Person-to-person by aerosolized respiratory droplets	Young adults and children; found in military camps, colleges, schools, and long-term care facilities	Rash, arthralgias, and neurologic symptoms	Association with cold autoimmune hemolytic anemia (presence of immunoglobulin M [IgM] antibody, low C3 and C4 levels)
Legionnaires disease *(L pneumoniae)*	Inhalation of aerosolized contaminated water sources, such as from air conditioning systems, hot tubs, and hospital ventilators	Adults over 50 years of age, hospitalized patients, persons who smoke	Gastrointestinal symptoms, relative bradycardia, and neurologic symptoms	Hypophosphatemia, hyponatremia, and renal dysfunction
Chlamydia pneumonia (*C pneumoniae)*	Person-to-person by aerosolized respiratory droplets	School-aged children and elderly patients; found in schools, military camps, prisons, and long-term care facilities	Laryngitis and persistent cough	Eosinophilia

Sources—References 10, 35–41.

among the most common viruses responsible for CAP in humans. Viruses are also frequently the cause of severe pneumonia, community outbreaks, and worldwide pandemics of respiratory infection. Specific viruses responsible for major community outbreaks include avian influenza (H5, H7, and H9 viruses), severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), Middle East respiratory syndrome coronavirus (MERS-CoV), and most recently COVID-19 (27,32). While an animal source has been found as the initial vector of infection in all of these viral infections, these are generally not considered zoonotic infections.

During major outbreaks, person-to-person virus transmission through respiratory droplets does occur to a varying degree, least commonly with avian influenza virus. Hantavirus is not communicable from person to person and is considered a true zoonotic infection (33,34). Tables 1–6 summarize the microorganisms considered atypical and most commonly identified as the cause of atypical pneumonia, as well as the findings at radiography and CT.

Nonzoonotic Atypical Bacterial Pneumonias

Mycoplasma Pneumonia

Mycoplasma pneumonia, caused by the microorganism *M pneumoniae*, is one of the most common causes of CAP in children and young adults. Transmission of *M pneumoniae* is primarily person-to-person through respiratory droplets that are aerosolized during coughing or sneezing (35). Outbreaks of mycoplasma pneumonia are commonly seen in settings where people live or interact for prolonged periods of time in close quarters. *M pneumoniae* has been responsible for outbreaks of respiratory infection in long-term and elder care facilities, military camps, colleges, and schools (36,97).

The symptoms of mycoplasma pneumonia are similar to those of other forms of respiratory infection, including dry and wet cough, pharyngitis, sinus congestion, and low-grade fever (35). It is colloquially referred to as walking pneumonia, as symptoms are often milder than pneumonia from other causes. The incidence of fulminant mycoplasma pneumonia is rare, despite the high prevalence of *M pneumoniae* infection (98,99). The extrapulmonary manifestations of mycoplasma pneumonia are variable. However, neurologic symptoms, rash, and arthralgias are most commonly described (71).

The imaging findings of mycoplasma pneumonia are variable. Chest radiographs can be normal, although they most commonly demonstrate peribronchial cuffing and central predominant reticulonodular opacities resembling those depicted in viral infections. Focal distribution of reticulonodular opacities and lobar consolidation are less frequently described (71) (Fig 1a). Common imaging findings at CT are often bronchocentric and include perihilar ground-glass opacities, diffuse centrilobular micronodules, and bronchial wall thickening. Consolidation has been described

Table 2: Zoonotic Atypical Bacterial Pneumonias

Entity (Pathogen)	Zoonotic Reservoir	Transmission	Populations at Risk	Associated Clinical Findings	Laboratory Findings
Tularemia *(F tularensis)*	Rabbits, hares, rodents	Multiple modes: insect bites, inhalation of infectious aerosols, handling of infected animals, consumption of contaminated food or water	Individuals exposed to an infected animal	Tender adenopathy, ulcerations	Renal dysfunction
Psittacosis *(C psittaci)*	Birds	Direct contact or inhalation of aerosolized bird droppings	Veterinarians, owners of pet birds, employees of poultry processing plants	Severe headaches, gastrointestinal symptoms, encephalopathy, splenomegaly	Hyponatremia, renal dysfunction
Q fever *(C burnetii)*	Sheep, goats, cattle	Inhalation of aerosolized bacteria	Individuals who handle infected animals or are exposed to their habitat	If acute: fever, hepatitis, rash If chronic: endocarditis and osteomyelitis	Liver dysfunction

Sources.—References 42–51.

Table 3: Causes and Risk Factors for Viral Pneumonias in the General Population

Virus	Structure	Reservoir	Transmission	Populations at Risk
Influenza	Enveloped segmented negative-sense ssRNA, with helical capsid	Humans, pigs	Direct contact or inhalation of infected respiratory droplets	Elderly and immunocompromised patients, solid organ transplant recipients, pregnant women
Parainfluenza	Enveloped negative-sense ssRNA, with helical capsid	Humans	Direct contact or inhalation of infected respiratory droplets	Young children; elderly and immunocompromised patients, particularly lung and hematopoietic cell transplant recipients
RSV	Enveloped negative-sense ssRNA, with helical capsid	Humans	Direct contact or inhalation of infected respiratory droplets	Premature infants or children with congenital heart disease, chronic lung disease, or multiple or congenital abnormalities or who are immunocompromised
Adenovirus	Nonenveloped linear dsDNA	Humans	Direct contact or inhalation of infected respiratory droplets	Immunocompromised patients, persons in military camps or exposed to contaminated swimming pools
HMPV	Enveloped negative-sense ssRNA	Humans	Direct contact or inhalation of infected respiratory droplets	Young children and infants, prematurity

Sources.—References 52–58.
Note.—dsRNA = double-strand RNA, ssRNA = single-strand RNA.

in approximately one-third of patients with a lobular distribution (Fig 1b). Lymphadenopathy and pleural effusions are uncommon (101,102).

Legionella Pneumonia

Legionella pneumonia is caused by the genus *Legionella* and is responsible for up to 10%–15% of CAP cases (12). The clinical syndrome of legionella pneumonia and extrapulmonary manifestations was termed *Legionnaires disease* or *legionellosis* after a historic outbreak in 1976 during a convention of the American Legion in Philadelphia, Pa (72). *Legionella* spp are primarily aquatic microorganisms and, as such, outbreaks are commonly seen in the setting of aerosolized contaminated water sources, including household showers, air conditioning systems, hospital ventilators, hot tubs, cooling towers, and nebulizing respiratory devices. Although legionella pneumonia is mainly reported in patients who

Table 4: Causes and Risk Factors for Viral Pneumonias that Cause Community Outbreaks and Global Pandemics

Virus	Structure	Reservoir	Transmission	Population at Risk
Avian influenza viruses (influenza, H5, H7, H9)	Enveloped segmented negative-sense single-strand RNA (ssRSNA), with helical capsid	Birds	Direct contact with infected birds or poultry	Infants, elderly patients, individuals with chronic diseases
SARS-CoV-1	Enveloped positive sense linear ssRNA	Possibly bats	Direct contact or inhalation of infected respiratory droplets	Health care workers, elderly patients, pregnant patients
MERS-CoV	Enveloped positive-sense linear ssRNA	Camels	Direct contact or inhalation of infected respiratory droplets	Health care workers, persons with exposure to camels, patients with chronic disease
SARS-CoV-2	Enveloped positive-sense linear ssRNA	Not yet determined	Direct contact or inhalation of infected respiratory droplets	Elderly patients, patients with underlying chronic diseases, patients who are immunocompromised

Sources.—References 27, 28, 59–70.

are apparently immunocompetent, legionellosis is also well reported among patients who are immunocompromised, particularly those treated with antitumor necrosis factor-α therapy, patients with hematologic malignancy, and transplant patients. Additional risk factors include smoking and chronic lung disease, corticosteroid therapy, and treatment with cytotoxic chemotherapy (103).

Although most of the infections by nonzoonotic atypical microorganisms are sporadic and quantitatively more important in the outpatient setting, *Legionella* spp are known to represent an important cause of severe pneumonia in hospitalized patients (10).

Early symptoms of legionella pneumonia are similar to those of other pneumonias. Late and severe findings of legionella pneumonia include rapidly progressing respiratory and multiorgan system failure. Extrapulmonary manifestations commonly associated with *Legionella* spp infection include gastrointestinal distress (nausea, vomiting, diarrhea), relative bradycardia, and neurologic symptoms. Although nonspecific for legionella pneumonia, unexplained hypophosphatemia and hyponatremia are laboratory findings commonly associated with this pathogen (104). Legionella pneumonia is also associated with high and prolonged fever, which may persist despite adequate antimicrobial treatment.

While imaging findings of legionella pneumonia are widely variable and nonspecific, the most commonly initially observed finding is single lobe consolidation, with a predilection for the lower lobes (73). Rapid progression of multilobar opacities with asymmetric distribution is commonly described (Figs 2, 3). Unilateral pleural effusions are common (84). Imaging findings may persist beyond the expected 4–8 weeks time for resolution of typical pneumonia (105). Although legionella pneumonia may manifest with a wide variety of imaging findings, the presence of cavitation, hilar lymphadenopathy, hemothorax, or empyema are uncommon and argue against the diagnosis of *Legionella* CAP (104).

Chlamydia Pneumonia

Chlamydia pneumonia is caused by the microorganism *Chlamydophila pneumoniae* (also called *Chlamydia pneumoniae*). As with *M pneumoniae*, transmission occurs through respiratory droplets. The manifestation of laryngitis in chlamydia pneumonia has been cited as a distinguishing feature from mycoplasma or legionella pneumonia (35). Similar to those of mycoplasma pneumonia, outbreaks are thought to occur in crowded areas where there is prolonged exposure to individuals with infection such as schools, colleges, military camps, prisons, and nursing homes (38).

Chest radiographs most commonly depict unilobar involvement of patchy consolidation, with a predilection for the lower lobes (38,74,106). Pleural effusions and progression to multilobar involvement may be visualized. However, these features are not specific nor are they the predominant imaging pattern. Cavitation and lymphadenopathy are not characteristic features. CT images most often demonstrate an acinar pattern of ground-glass opacities in the lobe(s) involved (101). In contrast to mycoplasma pneumonia, centrilobular micronodules and bronchial wall thickening are much less frequently described. In addition, a reticular or linear pattern has been observed more frequently in chlamydia pneumonia compared with in pneumococcal pneumonia (85) (Figs 4, 5).

Table 5: Chest Radiographic Findings in Atypical Pneumonia

Type	Pathogen	Radiographic Findings: Lobar Consolidation	Reticulonodular Opacities	Peribronchial Cuffing	Pleural Effusion	Notes
Nonzoonotic	*M pneumoniae*	+	+++	+++	+	Possible to have effusions or adenopathy
	L pneumoniae	+++	−	−	+++	Unilateral pleural effusions are common
	C pneumoniae	++	+	−	+	Typically unilobar involvement, with patchy consolidation in lower lobes
Zoonotic	*F tularensis*	++	++	−	++	Variable appearance; can have single consolidations that resemble lung cancer
	C psittaci	++	+	−	−	Favors lower lobes
	C burnetii	++	++	−	−	Variable appearance; conflicting data on upper versus lower lobe predominance
Viral (general population)	Influenza	++	++	−	−	Bilateral opacities, with or without focal areas of consolidation
	Parainfluenza	++	++	−	−	Nonspecific; unilateral or bilateral consolidations
	RSV	++	+++	+	+	Nonspecific; can appear normal
	Adenovirus	++	+	+	−	Can resemble findings of bacterial pneumonia
	HMPV	++	+++	+	−	Variable depending on severity of infection
Viral (outbreaks)	Avian influenza	+++	++	−	+	Extensive pneumonic consolidation, mostly located in lower zones
	SARS-CoV-1	++	++	−	−	Findings can be unilateral or bilateral
	MERS-CoV	++	++	−	−	Predominance in periphery of lungs
	SARS–CoV-2	++	++	−	−	Subpleural areas of consolidation

Sources.—References 8, 11, 19, 27, 30, 48, 50, 71–83.
Note.—Plus sign indicates relative frequency of the findings, from lowest (+) to highest (+++). Negative sign (−) indicates that those findings are absent.

Zoonotic Atypical Bacterial Pneumonias

The atypical pneumonias of zoonotic origin are uncommon entities in the general population. Once an atypical pneumonia is suspected, the next diagnostic consideration is to differentiate zoonotic from nonzoonotic microorganisms. The clinical suspicion for zoonotic pneumonia is directly related to the patient's geographic location and exposure risk factors. The most common zoonotic agents infecting humans include *C psittaci, C burnetii,* and *F tularensis* (infections with these agents cause psittacosis, Q fever, and tularemia, respectively). If no exposure history to an animal vector is identified, it is extremely unlikely that the diagnosis includes a zoonotic atypical pneumonia (16).

Tularemia

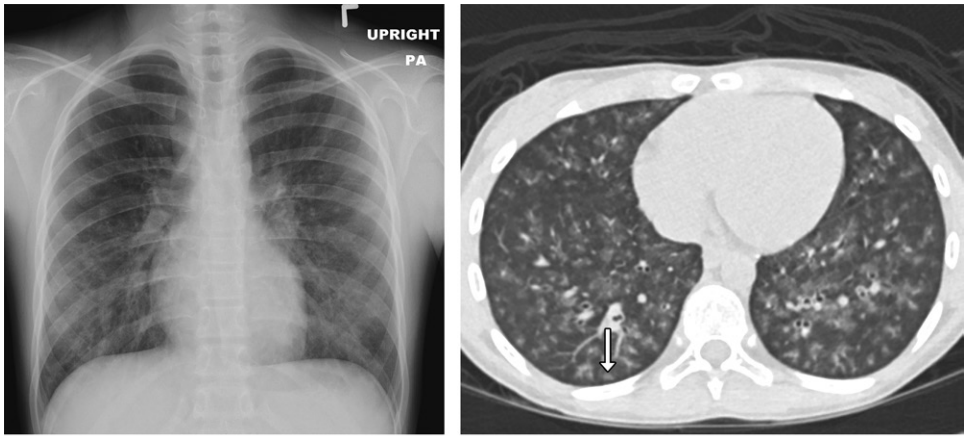
Pneumonic tularemia is a less common clinical manifestation of several subtypes of illness caused by the organism *F tularensis*. Although rabbits and rodents are commonly thought of as the main animal reservoir, *F tularensis* has been demonstrated in a multitude of animal species (42). Multiple routes of transmission have been described, including insect bites (wood tick, dog tick, lone star tick, deer flies), inhalation of infectious aerosols (those used in landscaping and construction), handling infected animals, drinking contaminated water, and laboratory work (43).

Tularemia is most commonly observed clinically as the ulceroglandular subtype, characterized by skin ulcers and lymphadenopathy (43).

Table 6: Chest CT Findings in Atypical Pneumonia

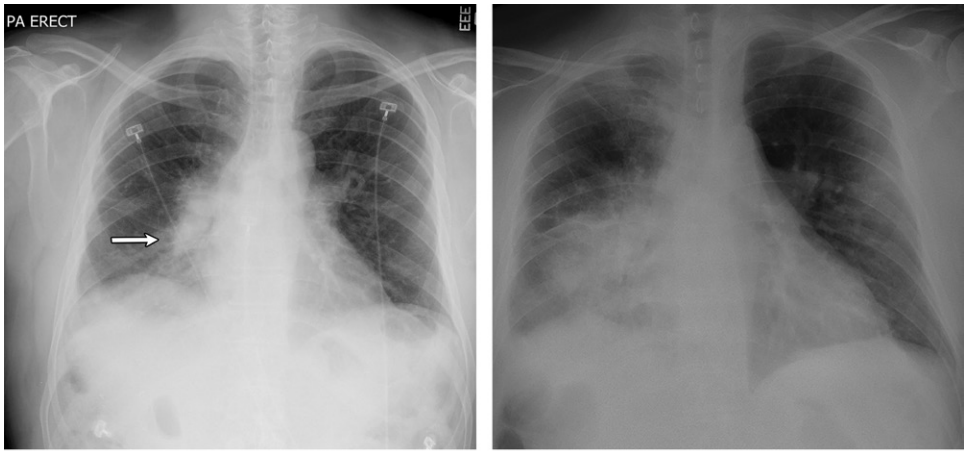
Type	Pathogen	CT Findings: Ground-Glass Opacity and Consolidation	CT Findings: Nodules, Micronodules, and Tree-in-Bud Opacities	CT Findings: Interlobular Septal Thickening	CT Findings: Bronchial and/or Bronchiolar Wall Thickening	Notes
Nonzoonotic	*M pneumoniae*	+++	+++	−	+++	Perihilar ground-glass opacities, diffuse centrilobular micronodules, bronchial wall thickening
	L pneumoniae	+++	−	−	−	Can progress from single lower lobe consolidation to multifocal asymmetric opacities; perihilar distribution with hilar adenopathy
	C pneumoniae	+++	−	+	−	Acinar pattern of ground-glass opacities; possible airway dilatation; lymphadenopathy is uncommon
Zoonotic	*F tularensis*	++	++	−	−	Patchy lobar or multilobar opacities; can have pleural effusions and prominent hilar and mediastinal lymphadenopathy
	C psittaci	++	−	−	−	Can range from normal-appearing to patchy or lobar consolidation
	C burnetii	++	++	−	−	Areas of nodular consolidation have been reported to demonstrate a ground-glass halo sign
Viral (general population)	Influenza	+++	+++	−	−	Bilateral reticulonodular areas of ground-glass opacities and centrilobular nodules, usually in the lower lobes
	Parainfluenza	+++	+++	−	−	Four variable imaging patterns (airway-centric disease, multifocal pneumonia, unifocal infection, and normal-appearing imaging examination)
	RSV	+++	+++	−	+++	Bilateral and asymmetric distribution
	Adenovirus	++	−	−	+++	Associated with bronchiectasis
	HMPV	+++	+++	−	−	Patchy areas of ground-glass attenuation, small nodules, tree-in-bud opacities, and multifocal areas of consolidation
Viral (outbreaks)	Avian influenza	+++	+	+	−	Can visualize consolidations with lobar collapse
	SARS-CoV-1	+++	−	+++	−	Crazy-paving pattern; no pleural effusions
	MERS- CoV	+++	−	+++	−	Crazy-paving pattern; can resemble cryptogenic organizing pneumonia
	SARS-CoV- 2	+++	−	+++	−	Crazy-paving pattern, subpleural consolidation

Sources.—References 8, 9, 11, 19, 27, 31, 48, 50, 71, 72, 74–79, 81, 82, 84–96.
Note.— Plus sign indicates relative frequency of the findings, from lowest (+) to highest (+++). Negative sign (−) indicates that those findings are absent.



a. b.

Figure 1. Mycoplasma pneumonia in a 12-year-old girl. **(a)** Posteroanterior (PA) chest radiograph shows bronchial wall thickening and mid and lower lung zone predominant heterogeneous opacities involving both lungs symmetrically. There is relative sparing of the lung apices. **(b)** Axial chest CT image (lung window) obtained at the level of the ventricles shows diffuse bilateral centrilobular nodules (arrow), peribronchovascular ground-glass opacities, and bronchial wall thickening, findings commonly seen in mycoplasma pneumonia. (Reprinted, with permission, from reference 100.)



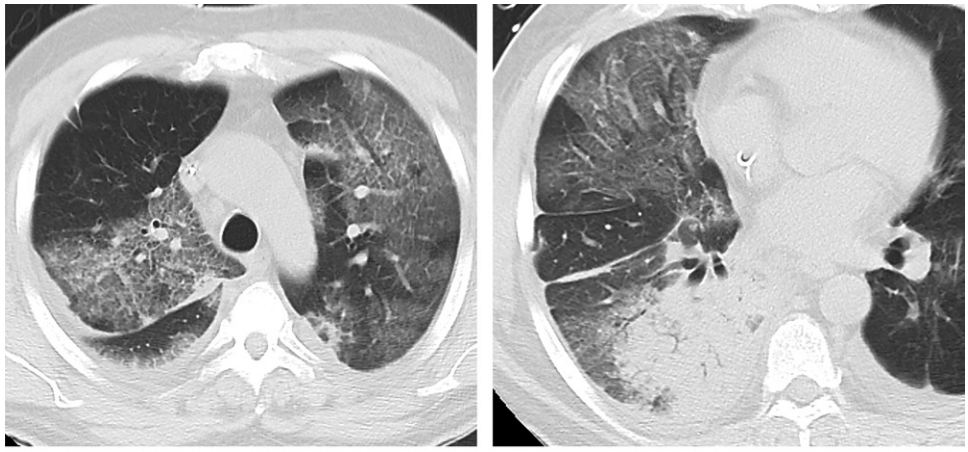
a. b.

Figure 2. Legionella pneumonia in a 58-year-old man with occupational exposure to a contaminated water source from crawling through vents at a refrigeration plant. **(a)** Initial chest radiograph obtained at onset of symptoms shows a right infrahilar and basilar consolidation (arrow). (Fig 2a reprinted, with permission, from reference 100.) **(b)** Follow-up chest radiograph obtained 2 days later shows progression of the right basilar consolidation and new consolidative opacities in the right upper lobe and periphery of the mid upper left lung, findings consistent with progressive multilobar pneumonia.

Pneumonic tularemia is infrequent and difficult to diagnose, as the clinical symptoms are similar to those of other types of pneumonia. Imaging findings of pneumonic tularemia are variable. Patchy, lobar, or multilobar consolidation and pulmonary nodules have been described (Fig 6). Single masslike consolidations that can simulate lung cancer have also been reported (75). The presence of pleural effusion and prominent hilar and mediastinal lymphadenopathy have frequently been reported (43). Resolution of radiographic findings may be prolonged, with an average time to resolution of 14 weeks.

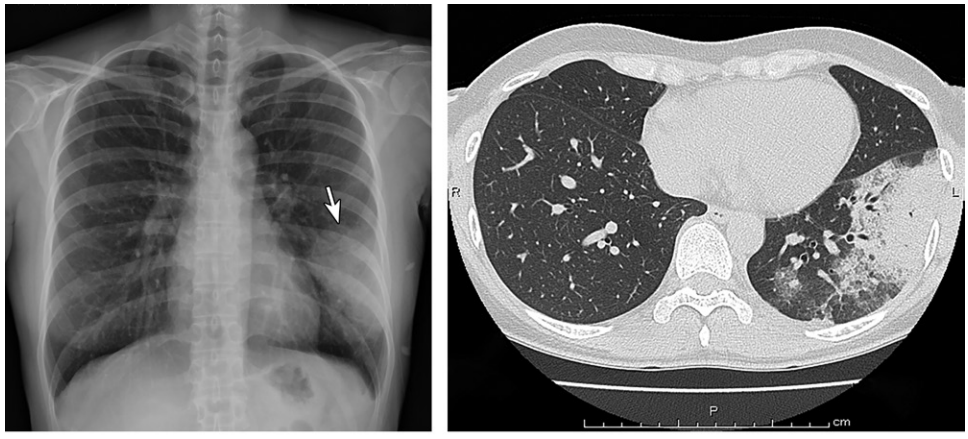
Psittacosis

Psittacosis, also known as parrot fever and ornithosis, is a rare cause of zoonotic atypical CAP, likely accounting for only 1% or less of all CAP cases, and is caused by the organism *Chlamydophila psittaci* (previously called *Chlamydia psittaci*) (44). The major risk factor is exposure to birds and aerosolized bird droppings (45). The United States Centers for Disease Control and Prevention recently announced a multistate psittacosis outbreak among poultry plant workers in the southeastern United States (107). Imaging findings are widely variable and range from normal findings at chest radiography to patchy or lobar consolidation. As with other



a. b.

Figure 3. Legionella pneumonia in a 58-year-old man with occupational exposure to a contaminated water source from crawling through vents at a refrigeration plant (same patient as in Fig. 2). Axial chest CT images (lung window) obtained at the level of the mid aortic arch **(a)** and left atrium **(b)** show multilobar ground-glass opacities and sublobar consolidation of the right lower lobe. Bilateral small-volume pleural effusions are present. (Fig 3b reprinted, with permission, from reference 100.)



a. b.

Figure 4. Chlamydia pneumonia in a 38-year-old woman. **(a)** PA chest radiograph shows a sublobar consolidation in the left lower lobe (arrow) with rounded morphology. (Fig 4a reprinted, with permission, from reference 100.) **(b)** Axial chest CT image (lung window) shows peripheral consolidation and ground-glass opacities characteristic of lobar pneumonia. No tree-in-bud micronodules or bronchial mucoid impaction are depicted. (Fig 4b courtesy of Takeshi Johkoh, MD, PhD, Kinki Central Hospital of Mutual Aid Association of Public Teachers, Hyogo, Japan.)

pneumonias, there appears to be a predilection for the lower lobes (60).

Q Fever

Q fever is caused by the bacterium *C burnetii* and is among the rarest causes of CAP. A range of domesticated (cats and dogs) and nondomesticated animals are reservoirs for *C burnetii* infection. Sheep, goats, and cattle are considered the major reservoirs for the organism. However, it has been found in a multitude of animals, including deer, mice, fish, and coyotes (47). Transmission is primarily through inhalation of aerosolized bacteria, which can be found in infected animal feces, birth products, or urine. Of note, *C burnetii* withstands drying and can remain viable in contaminated soil for several years (108).

The clinical manifestations of Q fever are widely variable, including both acute and chronic forms of the disease. Endocarditis and osteomyelitis have been reported as extrapulmonary complications of chronic Q fever. The imaging findings of Q fever consist of lobar, segmental, or nodular consolidations, bilateral interstitial thickening, and rarely pleural effusion (86,108,109).

Viral Pneumonias

The role of respiratory viruses as pathogens responsible for CAP has been underestimated

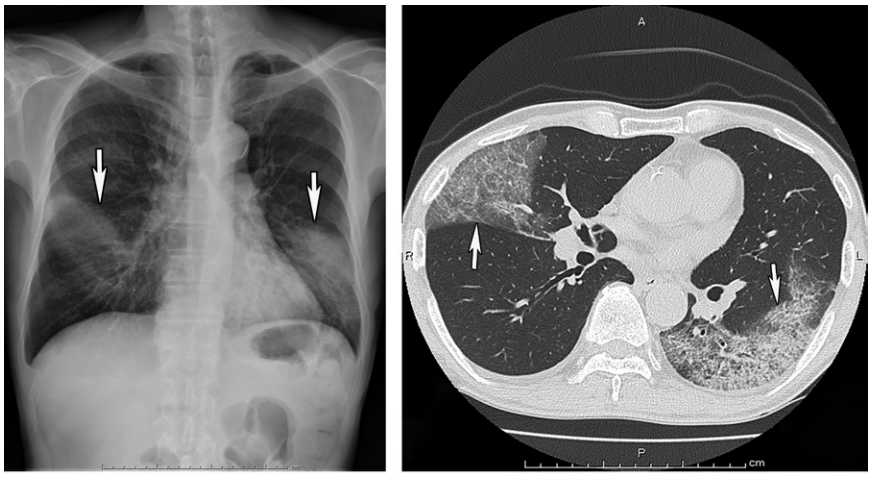
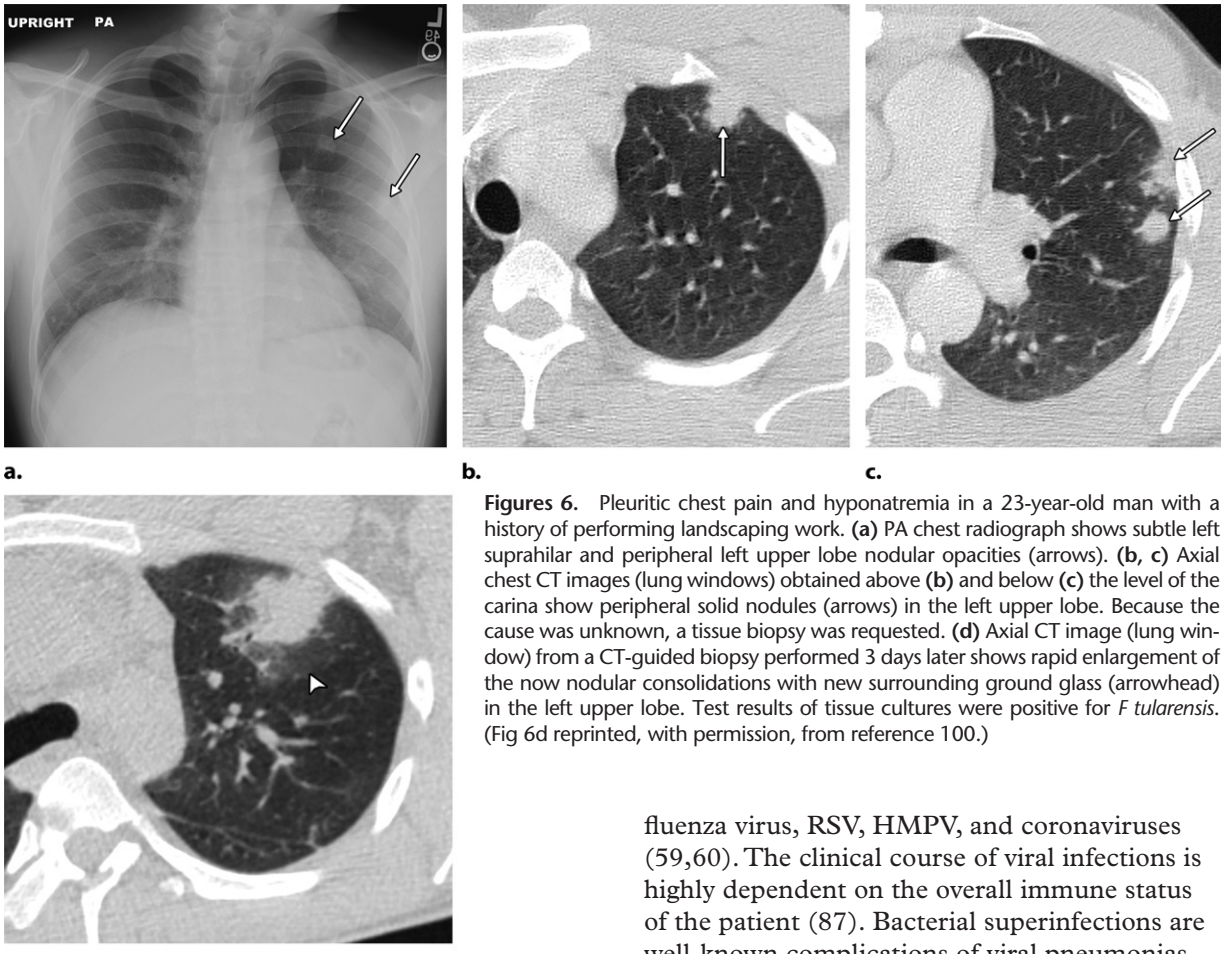


Figure 5. Chlamydia pneumonia in a 28-year-old man. **(a)** PA chest radiograph shows multifocal asymmetric consolidative opacities (arrows). **(b)** Axial chest CT image (lung window) at the level of the aortic root shows ground-glass opacities associated with minimal intralobular septal thickening (arrows) in the right middle and left lower lobes, consistent with multilobar pneumonia. (Courtesy of Takeshi Johkoh, MD, PhD, Kinki Central Hospital of Mutual Aid Association of Public Teachers, Hyogo, Japan.)



Figures 6. Pleuritic chest pain and hyponatremia in a 23-year-old man with a history of performing landscaping work. **(a)** PA chest radiograph shows subtle left suprahilar and peripheral left upper lobe nodular opacities (arrows). **(b, c)** Axial chest CT images (lung windows) obtained above **(b)** and below **(c)** the level of the carina show peripheral solid nodules (arrows) in the left upper lobe. Because the cause was unknown, a tissue biopsy was requested. **(d)** Axial CT image (lung window) from a CT-guided biopsy performed 3 days later shows rapid enlargement of the now nodular consolidations with new surrounding ground glass (arrowhead) in the left upper lobe. Test results of tissue cultures were positive for *F tularensis*. (Fig 6d reprinted, with permission, from reference 100.)

for many years. Respiratory viruses are a leading cause of morbidity and mortality worldwide, resulting in several forms of lower respiratory tract disease including tracheobronchitis, bronchiolitis, exacerbation of chronic pulmonary diseases, and severe pneumonia (52). Respiratory viruses that most commonly affect humans include adenovirus, influenza A and B viruses, parainfluenza virus, RSV, HMPV, and coronaviruses (59,60). The clinical course of viral infections is highly dependent on the overall immune status of the patient (87). Bacterial superinfections are well-known complications of viral pneumonias and can often be more serious than the viral infection itself (53).

Over the past decade, important diagnostic advances, specifically the use of rapid molecular testing, have greatly improved the ability to detect respiratory viruses in clinical specimens. The widespread use of reverse transcription–polymerase chain reaction (RT-PCR) or real-time RT-PCR by using RNA extracted from respiratory tract samples such as those collected from

a nasopharyngeal swab, sputum, deep tracheal aspirate, or bronchoalveolar lavage have allowed a more accurate assessment of the role that respiratory viral pathogens play in severe respiratory disease (110). Emerging viral infections represent a major global public health concern in the 21st century (111). A continued emergence of new viruses has been associated with regional outbreaks and pandemics in the past and present. In addition to the avian influenza A (H5N1) virus and influenza A (H1N1) (responsible for a 2009 pandemic), the emergence of highly transmissible viruses such as coronaviruses has re-emphasized the important role of respiratory viruses as causes of severe CAP (112,113).

Influenza Pneumonia

The influenza virus belongs to the *Orthomyxoviridae* family and is one of the most common human respiratory viruses. Influenza viruses are important human respiratory pathogens transmitted by the respiratory route and cause large epidemics, generally occurring during the winter in temperate climates (114). Influenza viruses have been classified into three distinct types: influenza A, influenza B, and influenza C.

The influenza A virus can be classified into subtypes on the basis of two surface proteins of the virus, which are the hemagglutinin (HA) and neuraminidase (NA), or H and N, respectively. Swine influenza caused by influenza type A virus includes subtypes H1N1, H1N2, H2N1, H3N1, H3N2, and H2N3. New influenza A virus subtypes sporadically emerge in humans, causing widespread disease or unpredictable pandemics. The worldwide spread of the greatest influenza pandemic, the so-called Spanish influenza in 1918, resulted in the deaths of approximately 50 million people (76,113).

Seasonal influenza A and B viruses are important human pathogens responsible for significant morbidity and mortality worldwide. In addition, influenza A zoonotic viruses are a constant pandemic threat. The two major surface glycoproteins, HA and NA, are linked to infectivity, transmissibility, virulence, host specificity, and resistance to antiviral treatment. The equilibrium between the HA binding affinity and the NA enzymatic activity (HA-NA functional balance) has to remain stable in human viruses to maintain good viral fitness. This balance is crucial in host adaptation, its role in viral evolution within the human population, and in antiviral resistance (115).

Both influenza and parainfluenza viruses are significant causes of respiratory illness in patients who are immunocompromised, including solid organ transplant recipients (54). Clinical symptoms resemble other lower respiratory tract diseases and pneumonia. The infection may progress rapidly to acute respiratory distress syndrome, multiorgan failure, and death. Influenza A pneumonia appears on CT images as bilateral reticulonodular areas of opacity with or without focal areas of consolidation, ground-glass opacities, and centrilobular nodules, usually in the lower lobes (77) (Fig 7).

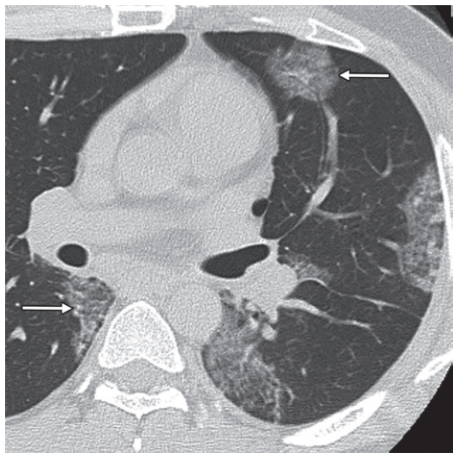
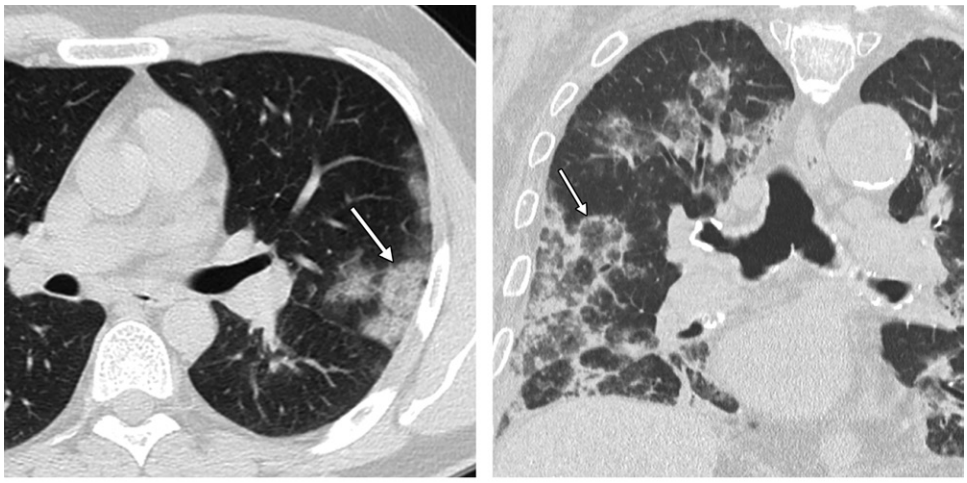


Figure 7. Influenza A virus infection in a 40-year-old woman with a history of acute cough, a recent onset of fever, and an equivocal chest radiograph (not shown). Axial chest CT image (lung window) shows peripheral focal ground-glass opacities (arrows) in the left upper lobe and both lower lobes.

Avian Influenza (H5N1) Pneumonia

Avian influenza pneumonia is caused by the H5N1 subtype of the influenza A virus (32). Despite their asymptomatic infection of wild birds, introduction of influenza A viruses into a new host such as terrestrial poultry species can cause severe illness, often leading to high mortality. Most human infections appear to be the result of close contact with infected birds, usually poultry or their products (61). Outbreak of a highly pathogenic influenza A (H5N1) virus among poultry was first reported in Hong Kong in 1997, which has continued to cause substantial numbers of human cases since that time. In recent years, the number of influenza A viruses crossing the animal-human host species barrier has increased (116,117).

The clinical findings and a history of close contact with poultry are helpful in identifying patients with influenza A (H5N1) pneumonia. Clinical manifestations are usually mild and restricted to the upper respiratory tract. In patients with chronic diseases or in elderly patients and infants, severe complications including hemorrhagic bronchitis, severe pneumonia (primary viral or secondary bacterial), respiratory distress syndrome (acute respiratory distress syndrome



a. b.

Figure 8. Variable imaging appearance of H1N1 swine influenza in two patients. **(a)** Axial chest CT image (lung window) in a 48-year-old man with infectious respiratory symptoms shows multifocal subpleural ground-glass opacities and consolidation in the left upper lobe (arrow). **(b)** Coronal CT reformatted image (lung window) in a 53-year-old man with severe shortness of breath, fever, and cough shows H1N1 pneumonia manifesting as an organizing pneumonia pattern, with subpleural and peribronchovascular consolidations. Note several areas of peripheral consolidation with central ground-glass opacities (arrow), the so-called reverse halo or atoll sign. While this specific sign is uncommon, other imaging features of organizing pneumonia manifest and are common in H1N1 pneumonia.

[ARDS]), and multiorgan failure may occur. The overall case fatality rate for influenza A (H5N1) infections exceeds 60% (62).

Most chest radiographs in patients with influenza A (H5N1) pneumonia are abnormal at the time of presentation, depicting extensive pneumonic consolidation with segmental and multifocal distribution, mostly located in the lower zones. The major CT abnormalities are consolidations; lobar collapse; focal, multifocal, or diffuse ground-glass opacities; interlobular septal thickening; small centrilobular nodules; and tree-in-bud opacities. However, the presence of tree-in-bud opacities in avian influenza and H1N1 influenza pneumonia is noted to be significantly less common than in most other influenza strains (19,78). Cavitation and pleural effusions are not common features of influenza pneumonia.

Swine Influenza (H1N1) Pneumonia

Novel swine-origin influenza A (H1N1) virus (S-OIV) was first reported in Mexico in April 2009 (118). Approximately 90% of confirmed infections were in individuals 40 years of age and younger. On June 11, 2009, the World Health Organization declared the first pandemic of the 21st century caused by swine-origin influenza virus A (H1N1) (119). The virus continues to spread globally, and its transmission among humans appears to be high, but its virulence is not greater than that observed with seasonal influenza.

Chest radiographic findings are similar to those of other viral pneumonias. The predominant CT findings are unilateral or bilateral ground-glass opacities, with or without associated focal or multifocal areas of consolidation. Cryptogenic organizing pneumonia is included in the radiologic differential diagnosis for the most common form of H1N1 presentation that exhibits subpleural or peribronchovascular ground-glass opacities or consolidations (Fig 8). Multifocal areas of air trapping may also be observed. Patients who progress to having more diffuse lung damage may demonstrate findings of ARDS (88,89).

Parainfluenza Pneumonia

Human parainfluenza viruses (HPIV) are single-stranded enveloped RNA viruses of the family *Paramyxoviridae* in the order *Mononegavirales*. HPIV bind and replicate in ciliated epithelial cells. They are common community-acquired respiratory pathogens and have been associated with most common types of seasonal upper respiratory tract infection in adults and children. Although parainfluenza types 1–4 are all respiratory pathogens in humans, types 1–3 are the most common cause of disease.

Pneumonia is the primary manifestation of lower respiratory tract infection in children over 5 years of age. The symptoms of HPIV begin with fever and are associated with otitis media, pharyngitis, conjunctivitis, croup, and tracheobronchitis. Chest radiography demonstrates nonspecific findings, including unilateral or bilateral consolidations. CT findings of HPIV are also variable, consisting of four imaging patterns: *(a)* airway-centric disease (bronchitis, bronchiolitis, or

bronchopneumonia), *(b)* multifocal pneumonia; *(c)* unifocal infection (single focal region of consolidation, ground-glass opacity, or tree-in-bud opacities), or *(d)* a normal examination, with no findings related to infection (90,120).

RSV Pneumonia

RSV is the most frequent viral cause of lower respiratory tract infection in infants. In an immunocompetent adult, RSV is estimated to cause 2%–5% of CAP cases, with elderly patients and patients with underlying cardiopulmonary disease at higher risk for severe infection (121,122). Chest radiographic findings in RSV pneumonia are nonspecific and resemble those of other viral pneumonias. Chest CT findings usually consist of a mixture of patterns, most commonly small centrilobular nodules, airspace consolidation, ground-glass opacities, bronchial wall thickening, and tree-in-bud opacities. The abnormalities are commonly distributed in the central and peripheral areas of the lungs and manifest with predominantly bilateral and asymmetric distribution (91).

Adenovirus Pneumonia

Human adenoviruses (HAV) are nonenveloped double-stranded DNA viruses, belonging to the genus *Mastadenovirus* of the *Adenoviridae* family. Humans are the reservoir for the adenoviruses that cause human disease. Adenovirus infections are more common in the winter and spring just after the influenza epidemic. These account for 5%–10% of acute respiratory infections in infants and children (123). In patients who are immunocompetent, depending on the serotype, most adenovirus infections are self-limited and cause mild respiratory disease with flulike symptoms (serotypes 1–3 and 7). Fatal infections can occur in patients who are immunocompromised, neonates, and occasionally in healthy children and adults (55).

Radiographic findings may be subtle and similar to those of other viral infections. At CT, HAV shows patchy bilateral areas of consolidation in a lobular or segmental distribution, resembling the appearance of bacterial pneumonia, and is more likely to manifest with consolidation compared with most other viral pathogens. Alternatively, HAV pneumonia may appear as bilateral multifocal ground-glass opacities, with a random distribution (79,80,92).

Human Metapneumovirus Pneumonia

HMPV, first identified in 2001, is a ubiquitous respiratory tract pathogen of the *Paramyxoviridae* family (genus *Metapneumovirus*) (56). HMPV is most frequent during the winter and cocirculates with other seasonal viruses, including influenza and RSV. HMPV has been implicated in outbreaks in hospitals and long-term care facilities for adults and children. HMPV can infect any age group but is most commonly seen in young children, particularly those younger than 2 years (56,57). Severe and sometimes fatal infections with a mortality rate of 10%–40% have been described in adults with chronic obstructive pulmonary disease, asthma, or cancer; residents of long-term care facilities; or those who have undergone lung transplantation.

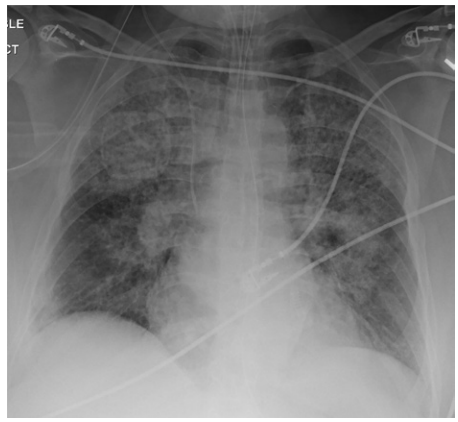


Figure 9. HMPV pneumonia in a 56-year-old woman with severe shortness of breath, cough, and fever who required treatment with respiratory support at hospital admission. Anteroposterior chest radiograph shows bilateral upper lobe predominant near-consolidative opacities involving both lungs. Bacterial microorganisms were not found. Test results confirmed HMPV pneumonia.

Chest radiographic findings range from normal to abnormal, according to the severity of the infection. Multifocal consolidations are depicted in cases of severe pneumonia (Fig 9). CT findings are variable but mostly consist of patchy areas of ground-glass attenuation, small nodules (<10 mm) with or without halo, tree-in-bud opacities, and multifocal areas of consolidation (81,93).

Coronaviruses

Coronaviruses are enveloped RNA viruses and members of the family *Coronaviriade*. The close association of animals and human hosts results in usually mild but occasionally severe community-acquired respiratory infections. Currently, six human coronaviruses have been identified (124). Four coronaviruses (human coronavirus NL63 [HCoV-NL63], human coronavirus 229E [HCoV-229E], human coronavirus OC43 [HCoV-OC43], and human coronavirus HKU1 [HKU1]) are prevalent and typically cause common cold symptoms in individuals who are immunocompetent (125). Three highly pathogenic viruses (SARS-CoV-1, SARS-CoV-2, and MERS-CoV) are zoonotic in origin and have

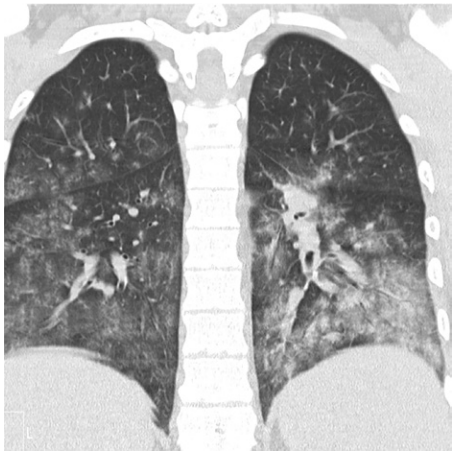


Figure 10. Coronal CT reformatted image in a 48-year-old man with a history of SARS shows multifocal bilateral ground-glass opacities, acinar ground-glass nodules, and left lower lobe consolidation. Note the absence of pleural effusions.

been linked to severe respiratory distress syndrome (126).

After the outbreak of severe acute respiratory distress syndrome (SARS), the emergence of Middle East respiratory syndrome (MERS), and the recent SARS-CoV-2 pandemic in 2019, coronaviruses have received worldwide attention as important pathogens in the cause of severe CAP (126,127).

Severe Acute Respiratory Distress Syndrome.—SARS, caused by SARS-CoV-1, is a systemic infection that clinically manifests as progressive pneumonia. SARS-CoV-1 first emerged in 2002–2003 in Guangdong, China, as an atypical pneumonia marked by fever, headache, and pneumonia. This new coronavirus had not been previously identified in humans (128).

SARS-CoV-1 has an incubation period of 2–10 days. Early systemic symptoms are followed by dry cough or shortness of breath within 2–7 days. Approximately 25% of patients develop severe pulmonary disease that progresses to ARDS, most commonly in patients older than 50 years or with underlying comorbidities (129).

The imaging features of SARS-CoV-1 infection consist of unilateral or bilateral ground-glass opacities, focal unilateral or bilateral areas of consolidation, or a mixture of both. In the areas of ground-glass opacification, thickening of the intralobular interstitium or interlobular septa may be present. If marked septal thickening occurs, a crazy-paving appearance results (130) (Fig 10).

Middle East Respiratory Syndrome.—MERS is a viral disease caused by MERS-CoV and was first reported in Saudi Arabia and the Middle East in 2012 (131). In May 2015, a large outbreak of MERS occurred in South Korea. Most patients developed a severe acute respiratory illness with symptoms of cough, fever, and dyspnea, resulting in a high case-fatality rate of 30%–40%. MERS progresses more rapidly to respiratory failure than does SARS and induces acute kidney injury. Approximately 20% of all virus cases were identified in health care workers and persons who come into close contact with camels (132).

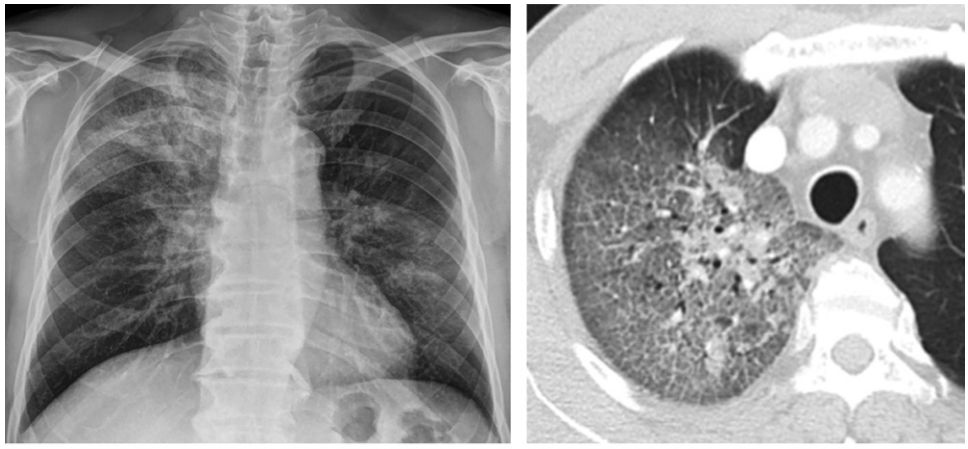
The clinical manifestations of MERS-CoV infections range from asymptomatic infection to mild, moderate, and severe disease, often complicated by severe pneumonia, ARDS, septic shock, and multiorgan failure including acute renal failure and severe hematologic disturbances (63).

Radiographs in the initial stages of the disease show pulmonary opacities and consolidation, with a peripheral and peribronchovascular predominance, in the mid and lower lung zones, and with more extensive ground-glass opacities than consolidation. The subpleural and peribronchovascular predilection of the abnormalities is suggestive of an organizing pneumonia pattern. Poorly defined patchy or nodular areas of consolidation are frequently observed in the periphery of the lungs, which then become diffuse (94) (Fig 11).

Coronavirus Disease 2019.—In December 2019, a cluster of pneumonia cases caused by a newly identified β-coronavirus occurred in Wuhan, China. The World Health Organization (WHO) initially named this coronavirus as the novel coronavirus (2019-nCoV) (64). On January 2020, WHO officially named the disease COVID-19 (133), and the Coronavirus Study Group of the International Committee proposed to name the new coronavirus as SARS-CoV-2, both issued on February 11, 2020 (65). The COVID-19 outbreak rapidly evolved into a pandemic, with approximately 23 464 600 diagnosed global cases and 809 591 related global deaths worldwide as of this writing (66).

The classic clinical picture of COVID-19 is that of a flulike syndrome of mild severity in most cases, but in 15% of cases it is complicated by interstitial pneumonia and a variable degree of respiratory failure associated with progression to ARDS (67) and multiorgan dysfunction in high-risk patients. The pathologic features of COVID-19 are similar to those of SARS and MERS. Pulmonary parenchymal involvement may result in bilateral diffuse alveolar damage with cellular fibromyxoid exudates, desquamation of pneumocytes, and hyaline membrane formation, suggestive of early phase ARDS.

Chest radiographs in patients with COVID-19 may be normal in early and/or mild disease. Abnormal radiographs have been reported in 69%



a. b.

Figure 11. MERS in a 45-year-old man. **(a)** PA chest radiograph shows right upper lobe and bilateral perihilar heterogeneous and consolidative opacities suspicious for multifocal pneumonia. **(b)** Axial chest CT image (lung window) focused on the right upper lobe shows sublobar ground-glass opacities and smooth interlobular septal thickening, which result in a crazy-paving pattern.

of patients at the initial time of patient admission. Findings are most extensive in range 10–12 days following symptom onset. Chest radiographs show multifocal peripheral or subpleural areas of consolidation, patchy ground-glass opacities, and ill-defined nodular consolidations of variable sizes that may become confluent over time (82).

The most frequent CT findings, especially in patients without severe respiratory disease, consist of ground-glass opacities, crazy-paving pattern, and consolidation, predominantly in a subpleural distribution in the lower lobes (83). Cavitation, micronodules, tree-in-bud nodules, and pleural effusions have not been reported (95,96). Temporal stages at CT have been reported, and the Radiological Society of North America has released a standard reporting language guideline (31,134). Overall, the imaging findings are similar to those reported for SARS-CoV-1 and MERS-CoV infections (Figs 12–14).

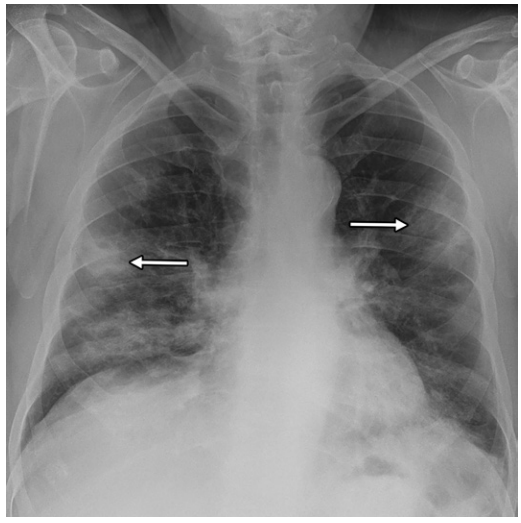
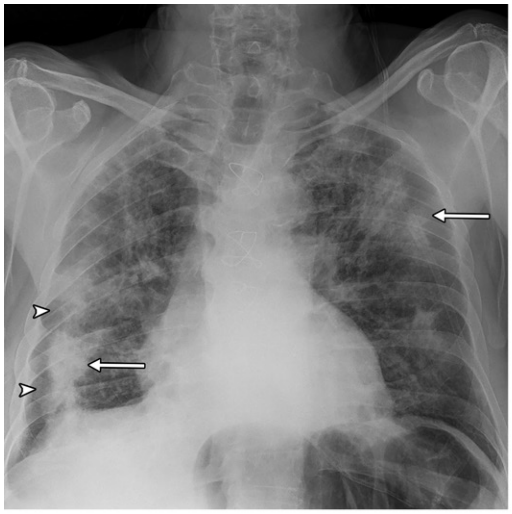


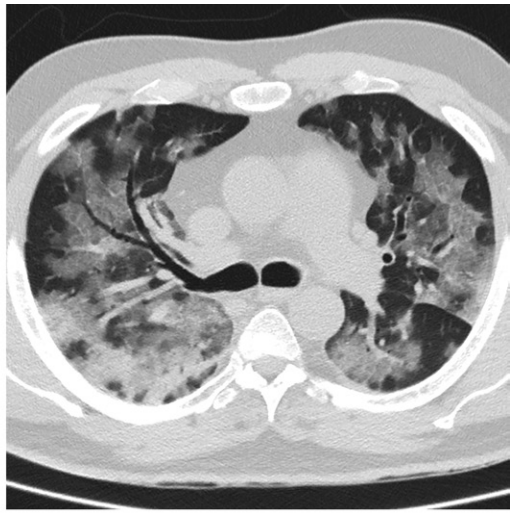
Figure 12. PA chest radiograph in a 58-year-old man with shortness of breath, cough, and fever and a positive contact history with COVID-19 shows peripheral predominant consolidative opacities involving both lungs (arrows). The findings are highly suggestive of viral pneumonia in COVID-19 in the setting of a high prevalence of SARS-CoV-2 infection within the community.

Imaging Atypical Pneumonias

There is controversy regarding the role of imaging, specifically of chest radiography, in the management of acute respiratory infections. The indications for chest radiography in the initial diagnosis and follow-up after treatment in specific patient populations are variable, specifically in patients who are immunocompetent (11). British, Canadian, American, and Japanese guidelines for the management of community-acquired pneumonia consider the use of chest radiography in the initial diagnosis of pneumonia as generally appropriate, with some variability among clinical scenarios, although not all of them agree about the role of imaging after treatment (6,11,13,135). Similarly, the indications to further assess disease with cross-sectional imaging, mainly CT of the chest, are variable among patient populations and society guidelines. The main advantages of CT in the setting of pneumonia are increased diagnostic sensitivity and the ability to better characterize complications that may impact patient management (8,9,11,136).

The imaging algorithm for the diagnosis of CAP is variable and accounts for both the clinical scenario and the environmental risk factors. The American College of Radiology (ACR) Appropriateness Criteria for acute respiratory illness in immunocompetent individuals (11) provides guidelines for the imaging of patients in various scenarios. Chest radiography is the first imag-





13. **14.**

Figures 13, 14. **(13)** Imaging findings in a 69-year-old man in a nursing home with recent onset of fever, cough, and shortness of breath during the COVID-19 pandemic. Anteroposterior chest radiograph shows upper, mid, and basilar peripheral consolidations (arrows) with subpleural sparing (arrowheads), an imaging pattern found with severe coronavirus infections (SARS, MERS, and COVID-19). RT-PCR test results were positive for COVID-19. **(14)** Axial chest CT image (lung window) in a 43-year-old man with shortness of breath and fever during the COVID-19 pandemic shows symmetric bilateral ground-glass opacities with central predominance, indeterminate imaging features that can be seen with COVID-19 pneumonia. RT-PCR test results were positive for SARS-CoV-2.

ing modality indicated in the diagnostic imaging workup of respiratory infections and, with minimal variability, is considered usually appropriate as the initial diagnostic test in the various scenarios of CAP (10,11). The role of chest CT in the diagnosis of CAP is limited to specific clinical scenarios and does not precede chest radiography in any case. Chest CT is not considered appropriate as an initial imaging examination in patients with low or high pretest probability of pneumonia (11).

Despite the wide overlap between imaging findings in pneumonia caused by typical and atypical microorganisms, the possibility of atypical pneumonia can be raised by the presence of unusual findings on a chest radiograph in a patient presenting with infectious respiratory and systemic symptoms. Either absent or minimal imaging findings on an initial chest radiograph despite positive clinical symptoms or an unusual distribution of the pulmonary opacities should raise the question of an atypical microorganism as a potential cause of the respiratory infection. Once suspected either clinically or radiologically, the diagnosis of atypical pneumonia requires a careful review of the patient's clinical manifestations, exposure risk factors, and laboratory workup test results to narrow the diagnostic possibilities and define the next steps in management.

Chest CT plays a relevant role in the diagnosis of patients with atypical pneumonia with normal or equivocal chest radiographic findings. Considering that CT can more accurately depict signs of infection (137), the indications for CT in patients with suspected atypical pneumonia may be wider and beyond the depiction of pulmonary complications. As microbiologic isolation of atypical microorganisms is challenging and the clinical symptoms are nonspecific, the combination of environmental exposure information, risk factors, and imaging findings at CT can improve the diagnostic accuracy and allow early initial management. Although it was used temporarily during an initial shortage of PCR testing, chest CT proved to be a useful diagnostic tool during the initial stages of the COVID-19 outbreak (138). In the management algorithm for these patients, chest CT is currently mostly reserved for diagnosis of pulmonary complications (139) and is considered as a useful diagnostic imaging tool in specific clinical scenarios (17).

A specific and relevant consideration in the decision to pursue further imaging in a patient with suspicion for atypical pneumonia is the risk of transmission to uninfected individuals. Specifically, viruses responsible for community outbreaks and pandemics are characterized by high rates of human-to-human transmission by respiratory droplets (68). The decision to perform additional imaging examinations, once the disease is suspected, should take into account the necessary protective measurements to avoid further spread of the infection among patients and health care personnel involved in the care of patients. As a result and recent example of the considerations surrounding imaging in pneumonia caused by atypical microorganisms, the role of imaging in

the diagnosis of COVID-19 has been limited exclusively to patients with confirmed infection and worsening respiratory status and, in specific resource-limited settings, to aid in clinical triage in patients with moderate clinical compromise and high probability of infection. Imaging is not indicated in patients with suspected COVID-19 and mild clinical features unless they are at risk for disease progression (140).

The indication for imaging follow-up of CAP in general is variable and mostly defined on an individual basis. Among imaging guidelines, the indication and timing for repeat chest radiography or chest CT after completion of treatment are inconsistently reserved for high-risk patients and patients with suspected complications (1,11). Neither the ACR Appropriateness Criteria nor the Infectious Diseases Society of America–ATS official clinical guideline for the management of CAP recommends routine radiographic follow-up in patients with resolved respiratory symptoms after 5–7 days of treatment (3,11). Severe atypical pneumonia and infection by specific zoonotic microorganisms commonly demonstrate a slower posttreatment radiologic resolution than typical bacterial infections (75).

Conclusion

Atypical bacterial pneumonias comprise approximately 15% of CAP cases. Viral infections may constitute a similar percentage of CAP and still a larger proportion during epidemics. An evidenced-based approach to the diagnosis of pneumonia is difficult given the widely variable and constantly changing epidemiology of respiratory infections. Despite advances in diagnostic tests and antibiotic therapies, CAP continues to be among the leading causes of death globally.

The imaging appearance of atypical pneumonias is widely variable but often differs from the lobar consolidation found in typical bacterial pneumonias. In some cases, an imaging pattern (such as bronchial wall thickening and reticulonodular opacities commonly visualized with mycoplasma pneumonia) may be the first finding suggestive of an atypical microorganism. The role of imaging in the diagnosis of atypical pneumonia differs from typical CAP in that it may help confirm the possibility of pulmonary involvement in patients who present with unclear and multisystemic clinical symptoms. Imaging may raise the possibility of an atypical infection by depicting unusual patterns of disease and, in the unfortunate case of a global pandemic, can aid in the initial clinical triage of patients with high probability of infection in resource-limited settings. Although the microorganisms recognized as atypical are variable, we provide an updated list of the most common organisms involved in this type of CAP, with the goal of providing clarity to the definition of atypical pneumonia among the medical community, including radiologists, to raise awareness about the implications of the use of the term *atypical pneumonia* in radiologic reports. The diagnosis and management of atypical pathogens can vary widely, and prompt diagnosis and prevention of community spread of some atypical microorganisms can have a relevant impact on local, regional, and global health policies.

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