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Relevant Website

www.brit-thoracic.org.uk – The British Thoracic Society is formed by the amalgamation of British Thoracic Association and Thoracic Society. It includes medical practitioners, nurses, scientists, and any professional with an interest in respiratory disease.

Atypical

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Abstract

‘Atypical pneumonia’ refers to a clinical syndrome associated with pneumonia (typically mild, nonlobar) and diverse upper respiratory tract and extrapulmonary manifestations. Clinical features overlap with bacterial pneumonia, and co-infection

with both typical (e.g., *Streptococcus pneumoniae* or other bacteria) and atypical pathogens may occur. ‘Atypical’ pathogens include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* spp. In large epidemiological studies, *Mycoplasma pneumoniae* has been implicated in 2–18% of community-acquired pneumonias; *Chlamydia pneumoniae*, in 2–8%; *Legionella* sp., 1–4%. Atypical pathogens lack cell walls and are resistant to β -lactam antibiotics but are usually susceptible to tetracyclines, macrolides, ketolides, and fluoroquinolone antibiotics. In this article, we also review other unusual causes of pneumonia which are transmitted by insects or vectors (e.g., Rocky Mountain spotted fever, cat scratch fever, Q fever, ehrlichiosis, Lyme disease, and tularemia). These diverse organisms are not found on Gram stain, and diagnosis requires special culture techniques or serological assays. We review the salient clinical and laboratory features of these various disorders, and discuss diagnostic and therapeutic strategies.

Introduction

In 1938, Hobart Reimann described a group of patients with an initial mild respiratory illness, often accompanied by headache and sore throat, progressing to pneumonia without sputum production. Because this was a picture very different from the well-known presentation of acute pneumococcal pneumonia, Reimann coined the term ‘atypical pneumonia’ to describe these cases. His observation was confirmed by subsequent similar reports and it was noted that the etiologic agents for these illnesses were unidentifiable on Gram stain and not recovered by culture methods used at the time.

The evolution of diagnostic techniques eventually led to the identification of many of the causative pathogens of atypical pneumonia, including the most significant ones, *Mycoplasma*, *Chlamydia*, and *Legionella*. Clinical features of atypical and typical community-acquired pneumonia (CAP) overlap, and the etiology of CAP cannot be determined on demographic, clinical, or radiologic features. However, the term ‘atypical pneumonia’ remains a useful one and describes a clinical picture characterized by more pronounced systemic than respiratory symptoms, bilateral patchy or interstitial infiltrates on chest radiographs, and negative results on sputum Gram stain and routine cultures.

Atypical pathogens are being isolated with increasing frequency in CAP and may occur as co-infecting organisms with typical bacterial pathogens. Recent expert consensus statements recommend that empirical therapy for CAP should include coverage for atypical pathogens. In this article, we discuss many of the important microbes that cause atypical pneumonia, including epidemiology, clinical presentation, and therapy (see Table 1). Additional pathogens that can induce an ‘atypical pneumonia’ picture include viruses (e.g., influenza, adenovirus,

Table 1 Summary of atypical pneumonia agents

Organism	Transmission	Incubation	Treatment
<i>Mycoplasma pneumoniae</i>	Person to person	3 weeks	Macrolides, tetracyclines, fluoroquinolones, ketolides
<i>Chlamydia pneumoniae</i>	Person to person	3 weeks	Macrolides, tetracyclines, fluoroquinolones, ketolides
<i>Chlamydia psittaci</i>	Birds and domestic animals	5–15 days	Tetracyclines; erythromycin as alternative
<i>Rickettsia rickettsii</i>	Ticks	2–14 days	Tetracyclines or chloramphenicol
<i>Ehrlichia chaffeensis</i>	Ticks	1 week	Tetracyclines
<i>Anaplasma phagocytophila</i>	Ticks	1 week	Tetracyclines
<i>Coxiella burnetii</i>	Cattle, sheep, goats, cats	2–14 days	Tetracyclines; combination therapy with tetracyclines and hydroxychloroquine, rifampin, or fluoroquinolone for endocarditis
<i>Bartonella henselae</i>	Cats	3–10 days	Macrolides and tetracyclines
<i>Borrelia burgdorferi</i>	Ticks	1 week	Tetracyclines or amoxicillin; ceftriaxone for neurologic disease
<i>Francisella tularensis</i>	Rodents, rabbits, hares	2–10 days	Streptomycin

respiratory syncytial virus, severe acute respiratory syndrome (SARS)-associated coronavirus, and cytomegalovirus), certain fungi such as *Histoplasma capsulatum* and *Pneumocystis jiroveci* (formerly *P. carinii*). A discussion of these diverse pathogens is beyond the scope of this article.

Mycoplasma pneumoniae

Mycoplasma pneumoniae, tiny (125–150 nm) intracellular bacteria that lack cell walls and do not stain with the Gram stain, are implicated in 2–18% of CAP.

Epidemiology

M. pneumoniae is transmitted from person-to-person by infected respiratory droplets. The incubation period following exposure averages 3 weeks. Infections due to *M. pneumoniae* are endemic in densely populated areas, with cyclic increases that lead to epidemics. Attack rates are highest in children and adolescents and only 2–4% of infections occur in adults older than 65 years.

More severe cases may be found in immunosuppressed patients or those with sickle cell disease or asplenia.

Clinical Features

Illness due to *M. pneumoniae* is usually mild and self-limited. Most common symptoms include indolent onset, low-grade fever, malaise, headache, upper respiratory symptoms (e.g., rhinorrhea, sinusitis, and pharyngitis), and bronchitis. A protracted, hacking cough may occur. Shaking chills are rare. Pneumonia

develops in 3–10% of infected patients, but is rarely severe. However, co-infection with bacterial pathogens occurs in one-third or more of patients. Chest findings on physical examination are usually minimal. Chest radiographs typically demonstrate peribronchial thickening and interstitial infiltrates; frank consolidation is uncommon. Pleural effusions are noted in 5–20% of patients, but are typically small; empyema is rare. *M. pneumoniae* may elicit wheezing in nonasthmatics, but whether it has a pathogenic role in asthma is controversial. Extrapulmonary features may include hemolysis, skin rash, and arthralgias; gastrointestinal complaints are unusual. In children, bullous or hemorrhagic myringitis is noted in 5–18% of cases with *Mycoplasma* infections. Rare manifestations of *Mycoplasma* infections include involvement of the central nervous system (CNS) (1–7%) or heart (1%), and arthritis (<1%). Fatalities are rare.

Diagnosis

IgM antibodies to the I antigen on erythrocyte membranes produce a cold agglutinin response in 50–65% of patients with infections due to *M. pneumoniae*, but cold agglutinin responses are non-specific. Peripheral blood leukocyte count is normal in 75–90% of cases. Culturing *M. pneumoniae* is difficult as it requires 2–3 weeks, and is rarely performed. Confirmation of the diagnosis of the infection usually relies upon detecting complement-fixing (CF) antibodies. Positive results are defined by more than fourfold rise in antibody titer (acute to convalescent) and single titer $\geq 1:32$. Antibody titers rise 7–10 days after infection, and peak at 3–4 weeks. Newer

immunoassays may be more sensitive and specific than CF serologies. The IgM capture test is optimal to diagnose *M. pneumoniae* in children. An enzyme-linked immunoassay that detects IgG is preferred for adults as they may not elaborate an IgM response. As results are not available for 3–4 weeks, serologies are performed infrequently in clinical practice. However, they are invaluable for epidemiological investigations and tracking epidemics. Polymerase chain reaction (PCR) assays can detect genomic DNA in nasopharyngeal secretions and are highly specific and sensitive for *M. pneumoniae* in patients with respiratory tract infections. However, PCR is infrequently used, except for research epidemiologic studies.

Treatment

Penicillin and cephalosporin antibiotics are ineffective against *M. pneumoniae* due to the lack of a cell wall. Tetracyclines, macrolides, ketolides, and fluoroquinolone antibiotics are active *in vitro* against *M. pneumoniae*. Resistance to macrolides may occur due to point mutations in the 23S ribosomal gene, but is rare. Doxycycline (100 mg b.i.d.) is efficacious and cost-effective. A 7–10 days course of therapy is adequate. Rare immunological complications of *M. pneumoniae* infections such as hemolytic anemia or CNS disease may require concomitant treatment with corticosteroids or even plasmapheresis.

Chlamydia Species

Chlamydia species are small, Gram-negative obligate intracellular parasites of animals and humans. Three species of *Chlamydia* cause human disease including: *C. trachomatis* (the cause of trachoma, oculogenital infection, and lymphogranuloma venereum); *C. pneumoniae* (a cause of respiratory infection); and *C. psittaci* (an avian pathogen for which man is an incidental host). The discussion in this article is limited to *C. pneumoniae* and *C. psittaci*.

Chlamydia pneumoniae

C. pneumoniae, formerly termed TWAR (after the laboratory designations of the initial isolates), was first identified as a respiratory pathogen in 1983. Serological studies implicate *C. pneumoniae* as the cause of 2–8% of community-acquired pneumonias.

Epidemiology Humans are the only known reservoir of *C. pneumoniae*. Transmission of infection is via respiratory secretions and the incubation period may be prolonged (up to several weeks). Seropositivity rates rise quickly during childhood

after age 5, with antibodies present in 50% of individuals by age 20, and a continued gradual rise in seropositivity till the age of 80. Epidemics have been described in military barracks, schools, and nursing homes. Infections due to *C. pneumoniae* are a significant cause of morbidity among the elderly.

Clinical features The vast majority (90%) of infections due to *C. pneumoniae* are asymptomatic or associated with mild, upper respiratory tract symptoms (headache, laryngitis, pharyngitis, sinusitis). Bronchitis or pneumonia due to *C. pneumoniae* is usually mild and self-limited. However, severe (sometimes fatal) CAP has been described. Chest radiograph findings are non-specific but patchy, subsegmental infiltrates are most common and severe, multilobar involvement is rare. As with other atypical pneumonias, blood leukocyte counts are usually normal. Uncommon extrapulmonary manifestations of *C. pneumoniae* infections include meningoencephalitis, Guillain–Barre syndrome, arthritis, and myocarditis. Fatalities are rare.

Diagnosis Isolation of *C. pneumoniae* in cultures is difficult, and is not performed in most clinical laboratories. The diagnosis is usually made by seroconversion. The CF antibody test is most often used, but is non-specific, since this detects antigens shared among all *Chlamydia* species. A fourfold rise in CF antibodies against *Chlamydia* or a single titer of $\geq 1:64$ is considered evidence of acute infection. Microimmunofluorescence (MIF) is more specific, but is technically difficult and is performed only in research laboratories. Criteria for the diagnosis of acute *C. pneumoniae* by MIF include a single IgM titer of $\geq 1:16$, a fourfold rise in IgG titer (acute to convalescent), or a single IgG titer of $\geq 1:512$. In primary infections, IgM is evident at 3 weeks after the onset of symptoms, followed by the IgG response at 6–8 weeks. The immunologic response to infection with *C. pneumoniae* appears incompletely protective as re-infection can occur. Re-infections are associated with IgG responses (not IgM) after 1–2 weeks. Other diagnostic techniques for detecting *Chlamydia* infection include immunoassay (EIA), direct fluorescent antibody, and PCR. PCR can be applied to nasopharyngeal swabs, sputum, or bronchoalveolar lavage (BAL) fluid and is more sensitive than cultures.

Treatment Tetracyclines, macrolides, ketolides, and fluoroquinolone antibiotics are active *in vitro* against *C. pneumoniae*, and are recommended for treating symptomatic infections. Given the mild, self-limited

nature of the disease, there are limited data on the optimal agents or duration of therapy. Most experts recommend treating for 10–14 days, as responses to therapy may be slow.

Chlamydia psittaci

C. psittaci is a rare cause of pneumonia that occurs following exposure to infected birds. The pneumonia caused by *C. psittaci* is termed psittacosis, derived from the Greek word for parrot, but is more properly designated an ‘ornithosis’ as all birds, not just parrots, can carry and spread the infection.

Epidemiology Birds are the primary carriers of psittacosis and humans may be infected via aerosolized droplets from infected birds. Birds may be asymptomatic or obviously ill when infected with *C. psittaci*. Rarely, humans acquire infection from other animals (e.g., sheep, goats, cattle, horses, cats, and dogs). Psittacosis is an occupational hazard of veterinarians, aviary or pet shop employees, zoo personnel, farmers, and workers in poultry-processing plants.

Clinical features The incubation period of psittacosis ranges from 5 to 15 days. Clinical manifestations are varied, but include an abrupt onset of fever, headache (often severe), a flu-like syndrome, malaise, myalgias, anorexia, and a dry cough. The clinical course ranges from a mild illness to fulminant infection with multisystemic involvement. Pneumonia is common (>75%), but is usually mild and dyspnea occurs in <20% of infected patients. Fatal respiratory failure is a rare complication. Unusual extrapulmonary organ manifestations include CNS involvement, endocarditis or myocarditis, proteinuria, pancreatitis, hemolysis, and hepatosplenomegaly.

Diagnosis The diagnosis is suggested by a history of contact with birds. Cultures are difficult and dangerous and not recommended except in specialized laboratories. Paired acute and convalescent antibody tests are the mainstay of diagnosis. CF assays are most often used, but cannot differentiate *C. psittaci* from other *Chlamydia* species. The MIF assay is specific for *C. psittaci* but is available only in specialty laboratories. A fourfold rise in antibody titer or an IgM antibody $\geq 1:16$ are considered diagnostic. Other techniques (e.g., monoclonal antibody and PCR) have been developed, but are not readily available.

Treatment Doxycycline (100 mg b.i.d. for 10–14 days) is the treatment of choice for infections due to *C. psittaci*. Other options include macrolides, chloramphenicol, or fluoroquinolones.

Rickettsial and Related Diseases

The order Rickettsiales includes the families Rickettsiaceae and Ehrlichiaeae, and the family Rickettsiaceae formerly included organisms of the genus *Coxiella* and *Rochalimaea* (now known as *Bartonella*). Within these groups are a great number of human pathogens that are maintained in nature by both mammals and arthropod vectors. In this review, we restrict our discussion to a few select species including: *Rickettsia rickettsii* (the cause of Rocky Mountain spotted fever (RMSF) and the most common rickettsial disease in the US), *Ehrlichia chaffeensis* (the cause of Ehrlichiosis in the US), *Coxiella burnetti* (the cause of Q fever), and *Bartonella henselae* (the causative agent for cat scratch fever). In general, the diagnosis of infections due to these agents is based on epidemiologic exposure history and serologic testing.

Rocky Mountain Spotted Fever

Rickettsiae are Gram-negative coccobacillary obligate intracellular parasites and are spread by arthropod vectors (e.g., lice, fleas, mites, ticks). RMSF is the most severe and most often reported rickettsial illness in the US. It is caused by the bite of a tick infected with *Rickettsia rickettsii* and is a potentially lethal disease, particularly in young children.

Epidemiology RMSF is a misnomer as its distribution is not restricted to the Rocky Mountain region of the US. It occurs not only in the northern Rocky Mountain states, but also in the southeastern and south-central states, Cape Cod MA, Long Island NY, Mexico, Central America, and Latin America. The incubation period is 2–14 days following a tick bite. Most cases occur in the spring or summer. Approximately 1000 cases are reported annually in the US.

Clinical features Initial symptoms include fever (>95%), headache (90%), myalgias (80%), and nausea (60%). Abdominal pain may be a predominant feature. A typical rash develops between the 3rd to 5th day of the illness. The rash starts on the ankles and wrists, and spreads centrally to the palms and soles. A maculopapular eruption evolves to petechiae and a vacuolitic rash. Damage to small blood vessels may result in leakage of plasma, reduced blood

volume, and shock. With severe cases, bleeding, gangrene of the digits, thrombocytopenia, seizures, CNS signs, or renal failure may develop. The lung is not a primary target for *Rickettsiae rickettsii*. However, pulmonary infiltrates are present in one-third of cases; acute respiratory distress syndrome (ARDS) occurs in fewer than 10% of cases.

Diagnosis The diagnosis of RMSF is usually based upon the constellation of clinical features in the appropriate epidemiological setting. The diagnosis is usually confirmed serologically by indirect fluorescent antibody (IFA), which is available in state health departments or reference laboratories. Titers >1:64 are suggestive. Titer rises occur 7–14 days after the onset of illness, so treatment must be initiated prior to results of serologies. Biopsies of skin lesions (direct IF or immunoenzyme methods) establish the diagnosis in two-thirds of cases.

Treatment Tetracycline or chloramphenicol are preferred therapies. Prompt initiation of therapy is critical to avert serious complications and mortality. Delay >5 days of initiation of appropriate antimicrobial therapy has been associated with an increased mortality rate (23% versus 6% with early treatment).

Ehrlichiosis

Ehrlichiae are Gram-negative obligate intracellular bacteria that grow within membrane vacuoles in human and animal leukocytes. The two most important human ehrlichial diseases are human monocytic ehrlichiosis (HME), caused by *Ehrlichia chaffeensis*, and human granulocytic ehrlichiosis (HGE), caused by *Anaplasma phagocytophila* (previously known as *E. equi*, *E. phagocytophila*, and the agent of HGE). HME was first recognized in 1987; HGE was described in 1994.

Epidemiology *E. chaffeensis* is transmitted to man through tick bites. White-tailed deer are the principal animal hosts for *E. chaffeensis* while deer and the white-footed mouse are the principal animal hosts for *A. phagocytophila*. As with other tick-borne diseases, infections are most common in spring and summer. Tick bites, exposure to wildlife, and golfing have been implicated as risk factors for the disease.

Clinical features After a median of one week of infection with *Ehrlichia*, characteristic symptoms may develop including fever, headache, nausea, vomiting, myalgias, and anorexia. A maculopapular rash is present in 20–36% of patients with HME but is rare in HGE. Leukopenia and thrombocytopenia are

present in 50–90% of cases. Pulmonary infiltrates are present on chest radiographs in 40–75% of patients; ARDS occurs in 11–18%. Mortality rates range from 2 to 5% for HME and 7–10% for HGE.

Diagnosis Culture of *Ehrlichia* is extremely difficult. Examination of peripheral blood or buffy coat may reveal characteristic clusters of intraleukocytic inclusions (morulae). Morulae (Latin for ‘mulberries’) are seen in the cytoplasm of neutrophils in patients with HGE and in mononuclear cells in patients with HME. IFA tests are available in all state health departments for *E. chaffeensis*. The Centers for Disease Control (CDC) case definition of HME includes fourfold change in antibody titer (acute to convalescent) with a minimum titer of 1:64. IFA tests for HGE are available only in a few research laboratories. PCR tests are available for both HME and HGE.

Treatment Controlled studies are lacking, but tetracyclines are effective. Activity of chloramphenicol is variable. Rifampin displays *in vitro* activity against *Ehrlichia* and may have clinical utility. Doxycycline (100 mg b.i.d. for 10–14 days) is the preferred therapy.

Coxiella burnetii (Q fever)

Coxiella burnetii is a pleomorphic Gram-negative coccobacillus which causes Q fever, an acute febrile illness which may be complicated by pneumonia or hepatitis, or a chronic febrile illness which typically manifests as endocarditis.

Epidemiology Infection results from inhalation of organisms through exposure to infected livestock or unpasteurized milk. Q fever is endemic in some rural areas worldwide, but is rare in the US. Pneumonia due to acute Q fever can account for up to 7% of CAP in some regions (e.g., Nova Scotia, Switzerland, Spain, and Israel). *C. burnetii* is a potential bioterrorism agent, and is reportable in the US.

Clinical features Q fever is generally a mild illness; up to 50% of infected persons are asymptomatic. Manifestations are protean, but three syndromes are common: a self-limited, flu-like illness; pneumonia; and hepatitis. Hepatitis is more common in younger patients; pneumonia, in older immunocompromised patients. Severe pneumonia is rare and mortality is low (0.5–1.5%). Other manifestations of Q fever include rash (10%), myocarditis or pericarditis (1%), and meningitis or encephalitis (1%). Chronic forms of Q fever (lasting >6 months) occur in 1% of

infected patients. In this context, endocarditis is the most common manifestation.

Pathogenesis In chronic Q fever, high levels of antibodies and immune complexes may play a role in pathogenesis, eliciting tissue injury in the heart, arteries, bone, or liver.

Diagnosis Blood leukocyte counts are normal in 75% of cases; thrombocytopenia occurs in 25%. Liver enzymes are elevated in up to 85% of patients with acute Q fever. Serological studies (IgG and IgM antibodies against *C. burnetii*) are employed to confirm the diagnosis. Detectable serum IgM antibodies may be present within 7–15 days of onset of symptoms, and are present in 90% by the third week. Antibody titers subside over 12 months. Persistent or recrudescent antibodies suggest chronic infection.

Treatment Acute Q fever is usually mild, and spontaneously resolves within 2 weeks. Doxycycline (100 mg b.i.d. for 14 days) is the treatment of choice for patients with severe or persistent symptoms, or with impaired immune systems. The efficacy of erythromycin is controversial. Fluoroquinolones appear to be active. Anecdotal responses have been noted with lincomycin, cotrimoxazole, and chloramphenicol. For Q fever endocarditis, optimal therapy has not been elucidated, but combination therapy with at least two antimicrobials is recommended. In this context, doxycycline combined with hydroxychloroquine, a fluoroquinolone, or rifampin may be used.

Bartonella henselae

Bartonella henselae can cause cat scratch disease (CSD) in normal hosts and bacillary angiomatosis, bacillary peliosis, and persistent bacteremia in human immunodeficiency virus (HIV)-infected patients.

Epidemiology Domestic cats are the natural reservoir for *Bartonella henselae* – associated disease in humans. Illness may follow recent contact with domestic cats, usually involving a scratch or bite.

Clinical features Typical features of CSD include regional lymphadenopathy and fever; systemic illness may ensue. In immunocompromised patients, involvement of liver, spleen, or visceral lymph nodes is common. Lung involvement is uncommon.

Treatment In normal hosts, CSD usually resolves without therapy. Macrolides and doxycycline have excellent *in vitro* activity, and are recommended

for nonresolving infections or in immunocompromised hosts.

Other Tick-Borne Diseases

Lyme Disease

Borrelia burgdorferi, a spirochete transmitted to man via tick bites, is the cause of Lyme disease, the most common vector-borne disease in the US and Europe.

Epidemiology *B. burgdorferi* is transmitted by infected ticks, which are often carried by small mammals residing in wooded areas or parks. Human infections are most common in spring and summer, when outdoor activities are at a peak. The annual incidence of Lyme disease has been increasing in the US; nearly 41 000 cases of Lyme disease were reported to the Centers for Disease Control and Prevention during 2001–02. Ninety-five percent of these cases were from 12 states: Connecticut, Delaware, Rhode Island, Maine, Maryland, Massachusetts, Minnesota, New Jersey, New Hampshire, New York, Pennsylvania, and Wisconsin.

Clinical features Within 1 week of infection by *B. burgdorferi*, a characteristic macular rash, erythema migrans, develops at the site of the tick bite in 80% of patients. Early symptoms include fever, malaise, fatigue, headache, arthralgias, and myalgias. Respiratory involvement is unusual, but nonproductive cough can occur. Secondary skin lesions often develop within days of the initial EM lesion but resolve spontaneously within 4 weeks. However, disseminated disease with involvement of the joints, heart, or nervous system can occur weeks to months later. In the US, 15% of untreated patients developed neurologic abnormalities; cardiac complications were reported in 8%.

Diagnosis The diagnosis of Lyme disease is confirmed serologically. IgM antibodies against *B. burgdorferi* appear 3–6 weeks after infection and can be detected by ELISA or immunofluorescence assay. Positive results should be confirmed by Western blotting.

Treatment Oral tetracyclines or amoxicillin for 3–4 weeks are preferred therapy for Lyme disease. For most patients with Lyme disease, oral therapy is as effective as intravenous (IV) ceftriaxone. However, when meningitis or encephalopathy are present, IV ceftriaxone is recommended because of superior penetration into cerebrospinal fluid (CSF).

Tularemia

Tularemia is a zoonosis caused by *Francisella tularensis*, a small, Gram-negative coccobacillus found in rabbits, hares, rodents, and ticks.

Epidemiology Transmission to humans occurs via contact with infected animals or tick bites. Risk factors include: hunting, cleaning, or handling animal skins; ingesting poorly cooked wild animal meat; tick bites; laboratory exposure; contact with contaminated water, soil, or hay. An epidemic of primary pneumonic tularemia in Martha's Vineyard was linked to cutting brush and lawn-mowing. Most cases of tularemia occur in the summertime. Approximately 200–300 cases are reported annually in the US, predominantly in southern states.

Clinical features Clinical features vary from an asymptomatic infection to septic shock and death. Fever, chills, headache, and malaise develop after an incubation period of 2–10 days. Manifestations depend upon the route of inoculation, dose of the inoculum, and virulence of the organism. Type A *F. tularensis*, found predominantly in North America, is more virulent than type B which is found predominantly in Asia and Europe. Ulceroglandular tularemia is the most common form, occurring in 60–80% of cases. A single erythematous lesion with central ulceration is present at the site of the bite or inoculation; tender regional lymphadenopathy may also be present. Five other main forms of tularemia include glandular (lymphadenopathy), typhoidal (fever, chills, headache, abdominal pain), primary oropharyngeal, primary pneumonic, and oculoglandular.

Pneumonia can occur via airborne or hematogenous routes. Primary pneumonic tularemia results from inhalation of *F. tularensis*; it is the most severe form, with mortality up to 60% in the absence of treatment. Radiographic features of tularemic pneumonia include unilateral or bilateral infiltrates, hilar adenopathy, pleural effusions, and cavitary lesions. Rare complications of tularemia include pericarditis, meningitis, ARDS, rhabdomyolysis, and acute renal failure. Mortality associated with tularemia is 2–4%.

Diagnosis The diagnosis of tularemia is made on clinical grounds (i.e., exposure history, lack of response to β -lactam antibiotics). Cultures of blood, body fluids, or tissue are insensitive, as the organism is fastidious. The diagnosis is confirmed by serologic testing (a single titer of $\geq 1:16$, or a fourfold rise in agglutinating antibodies, or ELISA to *F. tularensis*).

Treatment Streptomycin (10 mg kg⁻¹ intramuscularly b.i.d. for 7–10 days) is highly efficacious (97% cure rate, with no relapses) and is the treatment of choice. Improvement is prompt, usually within 48 h of initiation of streptomycin therapy. Tetracyclines, gentamicin, and chloramphenicol may be effective, but clinical cure rates are lower (77–88%) and relapse rates higher (6–21%). Favorable responses have been noted with macrolides and fluoroquinolones; β -lactams are ineffective.

See also: **Pneumonia:** Overview and Epidemiology; Community Acquired Pneumonia, Bacterial and Other Common Pathogens; Fungal (Including Pathogens); Nosocomial; Mycobacterial. **Signs of Respiratory Disease:** Lung Sounds. **Stem Cells. Systemic Disease:** Sickle Cell Disease.

Further Reading

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Community Acquired Pneumonia, Bacterial and Other Common Pathogens

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Abstract

Community-acquired pneumonia (CAP) is the number one cause of death from infectious diseases in the US, and the patient population that is affected is becoming increasingly more complex due to the presence of chronic illness which is commonly managed in outpatients who are at risk for pneumonia. The number one pathogen causing CAP is pneumococcus, which is commonly resistant to multiple antibiotics, thus complicating management. Other common pathogens include atypical organisms (*Chlamydia pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*), *Hemophilus influenzae*, enteric Gram-negatives (especially in those with chronic illness and aspiration risk factors), and *Staphylococcus aureus*. Successful management requires careful assessment of disease severity so that a site-of-care decision can be made (outpatient, inpatient, intensive care unit), appropriate samples for diagnostic testing collected, and antibiotic therapy initiated in a timely and accurate fashion. Initial antibiotic therapy is empiric, but even with extensive diagnostic testing, less than half of all patients have an etiologic pathogen identified. All patients with CAP require therapy for pneumococcus, atypical pathogens, and other organisms, as dictated by the presence of specific risk factors. Because pneumonia has both short-term and long-term impact on mortality, it is also important to focus on prevention of this illness, which requires smoking cessation, and giving at-risk individuals both pneumococcal and influenza vaccines.

Introduction

Pneumonia, a respiratory infection of the alveolar space, can vary from a mild outpatient illness to a severe illness necessitating hospitalization and intensive care. It is the sixth leading cause of death in the US and the number one cause of death from infectious diseases. When the infection occurs in patients who are living in the community it is termed community-acquired pneumonia (CAP), while it is called nosocomial pneumonia if it arises in patients who are already in the hospital. Presently, the distinction between community-acquired and nosocomial infection is less clear because the 'community' includes