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CHLAMYDIA INFECTION AND RESPIRATORY DISORDERS

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Abstract. *Three chlamydial organisms are pathogenic to humans: C.pneumoniae, C.psittaci, and C.trachomatis. Clinical picture of chlamidiosis determine by species of the microbe. Efficiency of the treatment depends on timely and adequate therapy.*

Key words: *Chlamydia, pneumonia, infection.*

Three chlamydial organisms are pathogenic to humans: *Chlamydophila* (formerly *Chlamydia*) *pneumoniae*, *Chlamydophila* (formerly *Chlamydia*) *psittaci*, and *Chlamydia trachomatis*. These are small, gram-negative, obligate intracellular organisms. All 3 species can cause pneumonia in humans.

C. pneumoniae causes mild pneumonia or bronchitis in adolescents and young adults. Older adults may experience more severe disease and repeated infections.

C. psittaci causes psittacosis or ornithosis after exposure to infected birds. Ornithosis is the preferred term, because almost any bird can transmit the organism. The clinical spectrum of *C. psittaci* infection ranges from an asymptomatic infection to a fulminant toxic syndrome. Patients with ornithosis most commonly present with pneumonia or fever of unknown origin.

C. trachomatis is an important cause of sexually transmitted diseases, includingtrachoma, pelvic inflammatory disease, and cervicitis. *C. trachomatis* can also cause pneumonia, primarily in infants and young children. Reports document cases of pneumonia due to *C.trachomatis* in immunocompromised adults and laboratory workers.

Classification of pneumonia:

- Mycoplasma Pneumonia

- Bacterial Pneumonia
- Viral Pneumonia
- Imaging Pneumocystis Carinii Pneumonia
- Community-Acquired Pneumonia
- Nosocomial Pneumonia
- Ventilator-Associated Pneumonia
- Pneumocystis (carinii) jiroveci Pneumonia
- Fungal Pneumonia
- Pneumonia, Immunocompromised
- Aspiration Pneumonia
- Lymphocytic Interstitial Pneumonia
- Bacterial Pneumonia
- Atypical Bacterial Pneumonia
- Viral Pneumonia

Chlamydiae initiate infection by attaching to the outer membrane of susceptible host cells. The organism subsequently produces cytoplasmic inclusions in the infected cells, which then release the matured inclusions to infect adjacent cells.

The mode of transmission is different among the 3 species (*C. pneumoniae*, *C.psittaci*, *C.trachomatis*), but all can cause systemic disease by hematogenous spread. Respiratory secretions transmit. *C.pneumoniae* from human to human, whereas infected birds transmit *C.psittaci* to humans via the respiratory route through direct contact or aerosolization [1]. Birds known to cause ornithosis include cockatiels, parrots, parakeets, macaws, chickens, ducks, turkeys, pigeons, and sparrows, among others.

When pregnant women have a *C.trachomatis* infection of the cervix, the organism is transmitted when the infant passes through the infected birth canal. *C. trachomatis* infection may cause neonatal conjunctivitis, nasopharyngitis, otitis media, and pneumonitis. The tendency to chronic inflammation is typical, and chronic persistent infection may occur if neonatal infections remain untreated.

Epidemiology. The incidence and prevalence of the chlamydial pneumonias vary with the causative organism.

C. pneumoniae pneumonia. The estimated number of cases of *C pneumoniae* pneumonia in the United States is 300,000 cases per year, and the pathogen is estimated to cause 10-20% of community-acquired pneumonia (CAP) cases among adults [2,3]. Globally, an analysis using 2 comprehensive international databases showed that the incidence of CAP due to *C. pneumoniae* from 4337 patients was 8% in North America, 7% in Europe, 6% in Latin America, and 5% in Asia [4].

Although *C.pneumoniae* infections occur every year, epidemiologic studies suggest a 4-year cycle in the incidence of *C.pneumoniae* pneumonia. This disease is more common in males (60-90%) than in females, a difference possibly due to cigarette smoking, and the incidence of *C.pneumoniae* pneumonia is highest among elderly persons.

Although primary infection pneumonia is more common in persons aged 7-40 years, reinfection pneumonia is more common in elderly persons. Approximately 50% of young adults and 75% of elderly persons have serologic evidence of a previous infection.

C. psittaci pneumonia. Psittacosis was first reported in Europe in 1879. Anyone exposed to infected birds is at risk for infection with *C.psittaci*. This disease is found worldwide and year-round, with most cases being sporadic.

Cases of ornithosis in the United States declined after the introduction of antibiotic-laced bird feed and a quarantine period of 30 days for imported birds. From 2009-2013, 813 cases of psittacosis in humans were reported to the US Centers for Disease Control and Prevention (CDC) [5]. The Council of State and Territorial Epidemiologists revised the case definition for psittacosis in June 2009 to include more stringent laboratory criteria for confirmed and probable cases. As a result, only 4 cases of psittacosis were reported in 2010, as compared with an average of 16 (range: 9–25) cases reported from 2000-2009 [6]. Additional information about case

reporting of psittacosis can be found through the National Association of State Public Health Veterinarians.

Approximately 70% of the psittacosis cases with a known source of infection result from exposure to pet birds. The diagnosis of psittacosis can be difficult, and many more cases may occur that are not correctly diagnosed or reported.

C. trachomatis pneumonia. In infants, an estimated 12,000 cases of pneumonia due to *C trachomatis* occur each year, and Approximately 5-22% of pregnant women are thought to have *C. trachomatis* infection of the cervix; 30-50% of neonates born to infected mothers show culture evidence of infection. Of infected neonates, 15-25% present with clinical conjunctivitis and/or nasopharyngitis that in some cases develops into neonatal pneumonitis, and approximately 11-20% of infants born to infected mothers develop symptomatic pneumonia before age 8 weeks [7]. Adult cases have been reported in immunocompromised hosts.

Clinical picture. The evaluation of patients with suspected pneumonia caused by *C.pneumoniae*, *C.psittaci*, or *C.trachomatis* is discussed in this section.

C. pneumoniae pneumonia. The incubation period of *C.pneumoniae* pneumonia is approximately 3-4 weeks, with a usually gradual onset that may be biphasic. Although most infected persons are asymptomatic, and most have relatively mild respiratory illnesses, symptoms of bronchitis or pneumonia may follow upper respiratory tract symptoms (rhinitis, laryngitis, pharyngitis, sinusitis) in 1-4 weeks.

Sputum is usually scant, but cough is prominent, with possible prolonged symptoms such as persistent cough and malaise for weeks to months despite appropriate use of antibiotics. In addition, a history of hoarseness is more common in *C.pneumoniae* infection than in mycoplasmal infection or other pneumonias. Headache occurs in as many as 58% of cases and may be important as a nonclassic pneumonia finding.

Fever is more often present in the first few days than in 1 week or later, but it is less likely to be reported, as the fever is often absent by the time of clinical examination.

Pharyngeal erythema without exudate occurs in various atypical pneumonias; however, sinus percussion tenderness is more common with *C. pneumoniae* pneumonia than with other pneumonias.

Rhonchi and rales are present even in mild disease.

C.psittaci pneumonia. Exposure to birds, especially sick ones, is a clue to the diagnosis in a patient with pneumonia and splenomegaly. Pet shop employees and poultry industry workers are also at risk. Obtain an occupational and avocational history in all patients with community-acquired pneumonia (CAP).

The incubation period of *C.psittaci* pneumonia is 5-14 days or longer. Abrupt onset of constitutional symptoms is a common presentation in symptomatic patients. The severity of disease ranges from asymptomatic to severe pneumonia with systemic illness. A nonproductive cough has been observed in 50-80% of infected patients; however, this symptom is often absent initially. Chest pain is common, but pleuritic pain is rare. Auscultatory findings may be sparse and may underestimate the extent of pneumonia.

Fever is the most common symptom and may reach 39.4-40.5°C. Some patients may present with culture-negative endocarditis or fever of unknown origin. Defervescence is usually slow.

Photophobia, epistaxis, tinnitus, deafness, gastrointestinal (GI) symptoms, and arthralgia have been reported in less than half of patients.

Physical findings that suggest ornithosis include a pulse-temperature dissociation (fever without elevated pulse), which is also seen in Q fever, typhoid fever, and Legionnaires disease [9]; somnolence; splenomegaly; and an erythematous, blanching, maculopapular rash (Horder spots) in the presence of pneumonia. Rose spots look very similar to Horder spots and are observed in persons with typhoid fever.

Signs of meningitis or encephalitis, including focal neurologic deficits and seizures, may develop. In addition, signs of hepatitis, hemolytic anemia, disseminated intravascular coagulation, meningoencephalitis, or reactive arthritis may be observed,

as well as cutaneous manifestations, including Horder spots (rare), splinter hemorrhages, superficial venous thromboses, acrocyanosis, and erythema nodosum.

C. trachomatis pneumonia. In patients infected *C.trachomatis* with, nasal obstruction and discharge, cough, and tachypnea are present. Infants are usually symptomatic for 3 weeks or more before presentation.

Most patients are afebrile and only moderately ill. Scattered crackles with good breath sounds are characteristic, but wheezing is usually absent. Conjunctivitis and middle ear abnormality are present in half the infants with pneumonia.

Differential Diagnosis. The differential diagnosis of chlamydial pneumonias includes the following conditions:

- Influenza
- Legionnaires Disease
- Mycoplasma Infections
- Pneumonia, Bacterial
- Pneumonia, Fungal
- Pneumonia, Viral
- Psittacosis
- Q Fever
- Tuberculosis
- Tularemia
- Other disorders to consider include the following:
- *C. trachomatis* infant pneumonia
- Respiratory syncytial virus infection
- *Bordetella pertussis* infection
- Infection with other respiratory viruses
- Tests in Chlamydial Pneumonias

Laboratory studies for diagnosis of the chlamydial pneumonias vary with the causative organism.

C. pneumoniae pneumonia. The commonly used serologic criteria used to evaluate *C.pneumoniae* pneumonia are an IgM titer exceeding 1:16 or a 4-fold

increase in the immunoglobulin G (IgG) titer by microimmunofluorescence (MIF) [10]. However, serologic testing is poorly standardized and studies have shown poor reproducibility [11, 12, 13]. In addition, the presence of a single elevated IgG titer may not be reliable, because elderly patients can have persistently elevated IgG titers due to repeated infections.

The absence of detectable antibodies several weeks after the onset of infection does not exclude a diagnosis of acute *C.pneumoniae* pneumonia, because the IgM antibody response may take as long as 6 weeks, and the IgG antibody response may take as long as 8 weeks to appear in primary infections.

In some laboratories, a polymerase chain reaction (PCR) assay with pharyngeal swab, bronchoalveolar lavage, sputum, or tissue can be used to seek *C pneumoniae* – specific DNA. This is the most promising rapid test but remains experimental [14].

The Film Array Respiratory Panel is a multiplex PCR that detects common respiratory viruses in nasopharyngeal specimens. In 2012, the US Food and Drug Administration approved the addition of 2 corona viruses and 3 bacteria to the Panel, including *Chlamydophila pneumoniae*, *Bordetella pertussis*, and *Mycoplasma pneumonia*. The FilmArray Panel can now detect 17 viruses and 3 bacteria from a single sample [15]. Reported sensitivity and specificity were both 100% for *Chlamydophila pneumoniae* but fewer than 10 positive samples were available for analysis [16].

In one study, the accuracy of PCR was compared with that of MIF IgM during an outbreak of *C.pneumoniae*. PCR was less sensitive (68% vs 79%, respectively) but more specific than MIF IgM (93% vs 86%, respectively) [17].

Cell culture with oropharyngeal swabs is probably the best test to detect *C. pneumoniae*, but it requires specialized culture techniques and is performed only in research laboratories.

The white blood cell count is usually not elevated in *C.pneumoniae* infection. Alkaline phosphate levels may be elevated.

C. psittaci pneumonia. Single serum titers are insensitive and nonspecific. Confirmation with paired acute and convalescent sera is advised. Serologic tests are preferred, because culture is difficult and hazardous.

According to case definitions from the Centers for Disease Control and Prevention (CDC), a confirmed case involves any of the following [5]:

- isolation of the organism by culture. Compatible clinical illness with a 4-fold rise in CF or MIF antibodies against *C.psittaci* (to a reciprocal titer of 32 or greater by paired sera at least 2 wk apart)

- detection of an IgM titer of 16 or greater against *C.psittaci* by MIF.

The CDC defines a probable case as a compatible clinical illness that is epidemiologically linked to a confirmed case or that has a single antibody titer of 32 or greater by MIF or CF after the onset of symptoms. The CDC accepts human specimens for the diagnosis of *C. psittaci* infection [18].

A CF test can cross-react with *C.pneumoniae* and *C.trachomatis.* MIF and PCR assays can be used to distinguish *C.psittaci* infection from infection with other chlamydial species.

A third serum sample may be necessary to confirm the diagnosis, because antibiotic treatment can delay or diminish the antibody response. All serologic tests should be performed simultaneously at the same laboratory.

C.trachomatis pneumonia. Clinical findings suggest the diagnosis of *C. trachomatis* pneumonia; the presence of chlamydial inclusions or elementary bodies on Giemsa-stained smears of the conjunctivae or nasopharynx confirms the diagnosis.

Testing of the infants may show findings of elevated antichlamydial IgM titer. Peripheral eosinophilia and elevated serum immunoglobulin levels are characteristic. Screen the parents for chlamydia and other sexually transmitted diseases.

Chest Radiography. Chest radiographs of patients with *C. pneumoniae* pneumonia most commonly show a single subsegmental infiltrate that is mainly located in the lower lobes. Extensive consolidation is rare, although acute respiratory distress syndrome (ARDS) has been reported. No radiographic findings

are characteristic. Residual changes can be observed even after 3 months. Pleural effusion occurs in 20-25% of cases.

In *C.psittaci* pneumonia, consolidation in a single lower lobe is the most common finding. However, various findings have been observed, including patchy reticular infiltrates radiating from the hilum, a diffuse ground-glass appearance, and a miliary pattern. Pleural effusions are evident in as many as 50% of cases; however, the effusions are usually small and do not cause symptoms.

In cases of *C.trachomatis* pneumonia, chest radiographs show bilateral interstitial infiltrates with hyperinflation [8].

Histologic Findings. Intra-alveolar inflammation with a milder degree of interstitial reaction is a characteristic pathologic finding in the lungs of patients with chlamydial pneumonias. Alveolar-lining cells contain intracytoplasmic inclusions.

Antimicrobials in Chlamydial Pneumonias. The goals of pharmacotherapy are to eradicate infection, reduce morbidity, and prevent complications.

Tetracyclines and macrolides are the drugs of choice for chlamydial pneumonias [19]. Tetracyclines are bacteriostatic in nature; they work by inhibiting protein synthesis. As a class, tetracyclines have similar antimicrobial profiles, and cross-resistance is likely. Macrolides inhibit bacterial growth, possibly by blocking dissociation of peptidyl t-RNA from ribosomes, thus causing cessation of RNA-dependent protein synthesis.

Management of C.pneumoniae Pneumonia. Administer empiric treatment when mixed infections with other organisms are present (pneumococci, mycoplasmata, legionellae). The frequency of mixed infection can be as high as 60%. Clinicians must treat empirically, because rapid testing is not readily available, and antibiotic therapy is usually completed before the results of serology testing become available.

Severely ill hypoxemic patients require ventilatory support in an intensive care unit (ICU).

Drug of choice. Doxycycline is the treatment of choice, except in children younger than 9 years and in pregnant women. Treatment should be continued for at

least 10-14 days after defervescence. If symptoms persist, a second course with a different class of antibiotics is usually effective.

In inpatient settings, use doxycycline hyclate (100 mg iv). In outpatient settings, use doxycycline (100 mg per os) or tetracycline hydrochloride (500 mg per os).

Alternative drugs. Alternative agents include erythromycin (500 mg per os) and newer macrolides such as azithromycin (500 mg per os/iv for 7-10 days) and clarithromycin (500 mg - 1 g per os for 10 days). The newer macrolides are better tolerated than erythromycin, and shorter courses of the newer macrolides appear to be effective.

Telithromycin is the first antibiotic in a new class called ketolides and is approved for *C. pneumoniae* pneumonia by the US Food and Drug Administration (FDA). This agent is more expensive than doxycycline. Telithromycin is a potent inhibitor of CYP3A4 and can cause potentially dangerous increases in serum concentrations of simvastatin, lovastatin, atorvastatin, midazolam, and other drugs. If this agent is used, statins should be withheld for the duration of therapy. Hepatotoxicity (some fatal cases) has been reported. Telithromycin is contraindicated in patients with myasthenia gravis.

Fluoroquinolones, including levofloxacin (500 mg per os/iv for 10-14 days or 750 mg per os/iv for 5 days) and moxifloxacin (400 mg per os/iv for 10-14 days), also have some activity, although less than that of tetracyclines or macrolides.

Patient education and consultations. Educate patients about the possible protracted course of illness and about the need for re-treatment if symptoms recur or worsen.

Consultations with infectious disease and/or pulmonary specialists may be required if a patient needs hospitalization or does not respond to therapy.

Complications. Complications of *C.pneumoniae* infection include otitis, erythema nodosum, exacerbations of asthma, endocarditis, Guillain-Barré syndrome, and encephalitis. New-onset asthma has been also been observed. Complications

Complications of psittacosis include endocarditis, thrombophlebitis, myocarditis, thyroiditis, pancreatitis, hepatitis, renal failure, disseminated intravascular coagulation, and fetal death in infected pregnant women.

Although some studies clearly associate *C.pneumoniae* organisms with atheromatous plaques [20], multiple sclerosis, macular degeneration, Alzheimer disease, chronic fatigue syndrome, or sarcoidosis, the role of *C.pneumoniae* in the pathogenesis of these diseases remains to be established [19]. Antibiotic trials for coronary artery disease are not supportive of their role [21, 22].

Management of C. psittaci Pneumonia. Tetracycline (500 mg per os) or doxycycline (100 mg per os/iv) is the treatment of choice in the treatment of *C psittaci* pneumonia. Continue treatment for 10-21 days; a longer course to prevent relapse is controversial.

Azithromycin (250-500 mg per os for 7 days) is probably effective based on in vitro data and in vivo animal data.

Erythromycin is the alternative treatment, but this drug may be less efficacious in severe cases.

Severely ill hypoxemic patients require ventilatory support in an intensive care unit (ICU).

Prevention. The incidence of *C.pneumoniae* infection among military recruits during basic training is high, and weekly azithromycin prophylaxis was 58% effective in preventing the disease in this setting.

Past infection with *C.psittaci* does not confer immunity to the disease. For prevention of *C.psittaci* pneumonia, individuals should avoid dust from bird feathers and cage contents as well as avoid handling sick birds. Furthermore, imported psittacine birds must be treated for 45 days with a balanced feed containing chlortetracycline with 0.7% calcium. Refer infected birds or suspected sources to veterinarians.

Evaluate mothers of children infected with *C.trachomatis* and their sexual partners, and treat them appropriately. Repeated parental screening may be warranted in high-risk populations.

Prognosis. Outcomes in the chlamydial pneumonias depend on the causative organism and the disease severity.

C.pneumoniae pneumonia. Most cases of infection with *C. pneumoniae* are mild and usually respond to treatment in an outpatient setting. Patients with underlying disease or with concurrent infection (eg, pneumococcal bacteremia) can develop severe illness.

Treatment failure in *C.pneumoniae* pneumonia may occur more often with erythromycin [23]. Retreatment is often successful, especially with tetracyclines. Complete recovery is slow: cough and malaise may persist for weeks to months despite appropriate treatment.

C. psittaci pneumonia. *C.psittaci* infection is usually curable in 7-14 days with early diagnosis and treatment. A full recovery from *C.psittaci* pneumonia usually takes 6-8 weeks, and relapse may occur.

The mortality rate from infection with *C.psittaci* was 20% in the era before the advent of antibiotics. The mortality rate is 5% with antibiotic treatment; it is less than 1% with early diagnosis and treatment.

C. trachomatis pneumonia. Most infants with *C.trachomatis* pneumonia are only moderately ill and respond to appropriate antibiotics; if the infection is not treated, the clinical course may be protracted, and respiratory failure and prolonged spells of apnea may occur.

A higher-than-normal incidence of obstructive airway disease or asthma occurs in children who had chlamydial pneumonia before age 6 months.

Special Considerations. Avoid tetracyclines in pregnant women as well as in children younger than 9 years.

Infection with *C.pneumoniae* or *C.psittaci* can be fatal, especially in elderly patients with an underlying disease.

It is important to not only consider the diagnosis of *C.pneumoniae* infection in patients with bronchitis or community-acquired pneumonia (CAP) but also to treat with an appropriate antibiotic.

It is necessary to consider *C.psittaci* pneumonia in patients with CAP, especially those with bird exposure or fever of unknown origin, who are not responding to treatment. *C.psittaci* pneumonia must be reported to an appropriate health authority, and requests to a veterinarian should be made for evaluation and treatment of birds that are suspected sources of human infection.

In cases of infants with *C.trachomatis* infection, mothers and their sexual partners must be evaluated and treated appropriately. In younger children, *C.trachomatis* infection can also be acquired through sexual abuse.

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