78 Chlamydial Infections

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Definition/Classification

Chlamydiae are obligate intracellular bacteria that have established a unique niche within the host cell. They cause a variety of diseases in animal species at virtually all phylogenic levels. The genus has been reorganized with nine species: *Chlamydia trachomatis* and *C. pneumoniae*, which primarily cause disease in humans, and several species that have been split off from *C. psittaci* (Table 78.1). *C. psittaci* is primarily an avian pathogen, and is an important zoonosis in human. The new species include *C. pecorum*, which primarily infects cattle and other ruminants – there is no description of disease in humans; *C. muridarum* (formerly the agent of mouse pneumonitis – MoPn); *C. suis* (an important pathogen of swine); *C. abortus* (causes abortion in cattle and sheep, rarely has caused abortion in humans); *C. caviae* (formerly *C. psittaci* Guinea pig conjunctivitis strain); and *C. felis* (causes epidemic keratoconjunctivitis in cats).

All chlamydia species are characterized by a unique developmental cycle with morphologically distinct infectious and reproductive forms: the elementary body (EB) and reticulate body (RB). They have a gram-negative envelope without detectable peptidoglycan, although recent genomic analysis has revealed that both *C. trachomatis* and *C. pneumoniae* encode for proteins forming a nearly complete pathway for the synthesis of peptidoglycan, including penicillin-binding proteins. Chlamydiae also share a group-specific lipopolysaccharide (LPS) antigen and utilize host adenosine triphosphate (ATP) for the synthesis of chlamydial protein.

After infection, the infectious EBs, which are 200–400 μm in diameter, attach to the host cell by a process of electrostatic binding and are taken into the cell by endocytosis that does not depend on the microtubule system. Within the host cell, the EB remains within a membrane-lined phagosome. The phagosome does not fuse with the host cell lysosome. The inclusion membrane is devoid of host cell markers, but lipid markers traffic to the inclusion, which suggests functional interaction with the Golgi apparatus. The EBs then differentiate into RBs, which undergo binary fission. After approximately 36 h, RBs differentiate into EBs. At about 48–72 h, release may occur by cytolysis or by a process of exocytosis or extrusion of the whole inclusion, with the host cell left intact. Chlamydiae also may enter a persistent state after treatment with certain cytokines such as interferon gamma, treatment with antibiotics, or restriction of certain nutrients. While in the persistent state, metabolic activity is reduced. The ability to cause prolonged, often subclinical infection is one of the major characteristics of chlamydiae.

This chapter will cover infections in humans caused by *C. trachomatis*, *C. pneumoniae*, and *C. psittaci*.

Infections due to *Chlamydia trachomatis*

Etiology

C. trachomatis is an important cause of oculogenital infections in humans worldwide. There are 15 known serotypes that vary in tissue tropism and disease presentations.

Trachoma

Epidemiology

Trachoma is the most important preventable cause of blindness in the world. It is caused primarily by the A, B, Ba, and C serotypes of *C. trachomatis*. Blinding trachoma is believed to be endemic in 56 countries, mainly in sub-Saharan Africa, some areas of the Middle East, South and Southeast Asia, and in Aboriginal population in Australia. The disease is spread from eye to eye. Flies are a frequent vector. Poverty and lack of sanitation are important factors in the spread of trachoma. As socioeconomic conditions improve, the incidence of the disease decreases substantially.

Clinical Presentation/Pathology

Trachoma begins as a follicular conjunctivitis, usually in early childhood, often with copious purulent discharge. Active trachoma is seen predominantly in young children, becoming less frequent and shorter in duration with increasing age. Conjunctival scarring increases with age,

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_78,

Table 78.1
Classification of the genus *Chlamydia*

Species	Host(s)	Major diseases
Chlamydia trachomatis	Humans	Trachoma, urethritis, pelvic inflammatory disease, neonatal conjunctivitis and pneumonia, lymphogranuloma venereum
C. suis	Pigs	Gastrointestinal disease
C. muridarum	Mice	Pneumonia
C. pneumoniae	Humans	Pneumonia, bronchitis, exacerbations of asthma, asymptomatic infection
	Horse	
	Koalas	
	Bandicoots	
	Amphibians	
	Reptiles	
C. psittaci	Birds	Gastrointestinal disease
	Humans	Pneumonia (zoonosis)
C. abortus	Cattle	Abortion
	Sheep	
	Humans	Abortion (rare zoonosis)
C. pecorum	Cattle	Pneumonia, gastrointestinal disease, genital infections, conjunctivitis
	Sheep	
	Koalas	
C. felis	Cats	Keratoconjunctivitis
C. caviae	Guinea pigs	Conjunctivitis, genital Infections

not becoming evident until the second or third decade of life. Conjunctival scarring results in entropion, with the eyelid turning inward so that the lashes abrade the cornea, leading to corneal ulceration secondary to the constant trauma, eventually resulting in blindness. Bacterial superinfection may also contribute to scarring. The World Health Organization (WHO) suggests that at least two of the following four criteria must be present for a diagnosis of trachoma: (1) lymphoid follicles on the upper tarsal conjunctivae, (2) typical conjunctival scarring, (3) vascular pannus, and (4) limbal follicles.

Diagnosis

The diagnosis of trachoma is primarily clinical and can be confirmed by culture or NAATs for *C. trachomatis* performed during the active stage of disease. Serologic tests are not helpful clinically because of the long duration of the disease and the high seroprevalence in endemic populations.

Treatment/Prevention

The WHO currently recommends single-dose azithromycin (20 mg/kg, maximum 1 g) for the treatment of trachoma in children. Oral azithromycin is superior to treatment with topical antibiotics which require multiple dosing. Several studies conducted in trachoma endemic areas in several African countries have demonstrated that mass treatment with a single dose of azithromycin to all the residents of a village dramatically reduced the prevalence and intensity of infection. This effect continued for 2 years after treatment, probably by interrupting the transmission of ocular *C. trachomatis* infection.

Genital *Chlamydia trachomatis* Infections

Epidemiology

Genital chlamydial infections are caused by *C. trachomatis* serotypes D, E, F, G, H, I, J, and K. There are an estimated three million new cases of chlamydial sexually transmitted infections each year in the USA. In 2007, the overall rate of chlamydial infections in the USA among women (544.8 cases per 100,000) was almost three times the rate among men (190.4 cases per 100,000) (*Fig. 78.1*). Girls 15–19 years of age, had the highest rates of infection (3004.7 per 100,000) which is almost five times higher than in males in the same age group (615.0 per 100,000) (*Fig. 78.1*). This discrepancy is thought to be due in part to more extensive screening of women compared to men. However, with the introduction of noninvasive testing using urine, men are being tested more frequently. From 2003 through 2007, the rate of chlamydial infection in men increased by 43%.

Clinical Manifestations

Up to 75% of women with *C. trachomatis* cervical infection are asymptomatic. *C. trachomatis* can cause urethritis (acute urethral syndrome), epididymitis, cervicitis, salpingitis, proctitis, and pelvic inflammatory disease. The symptoms of chlamydial genital tract infections in men and women are less acute than those of gonorrhea, consisting of a discharge that is usually mucoid rather than purulent.

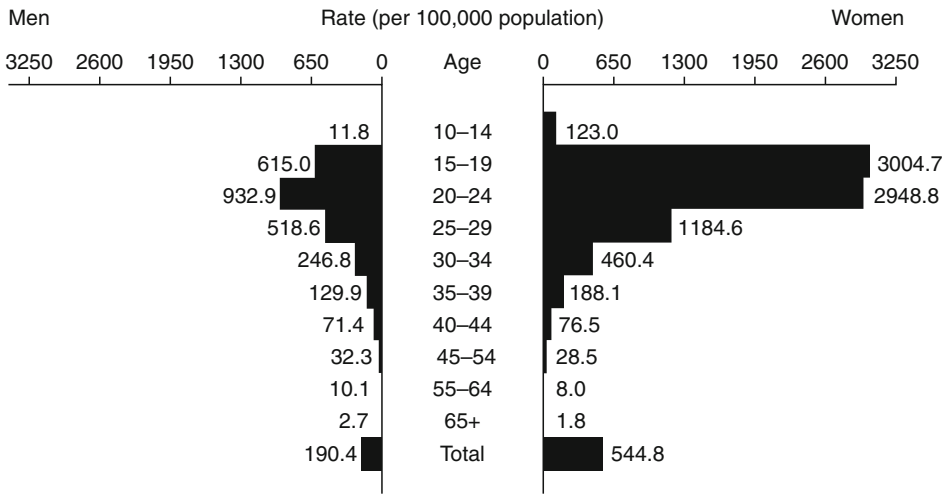

Figure 78.1
***Chlamydia trachomatis* – Age- and sex-specific rates: USA, 2007 (Reproduced from Centers for Disease Control and Prevention (2008) Sexually transmitted disease surveillance, 2007. U.S. Department of Health and Human Services, Atlanta, GA; December 2008) http://www.cdc.gov/std/pubs/**

In men, *C. trachomatis* can cause urethritis, proctitis, and epididymitis. Asymptomatic urethral infection is frequent in sexually active men. Autoinoculation from the genital tract to the eyes can lead to concomitant inclusion conjunctivitis.

Diagnosis

Diagnosis of genital chlamydial infection can be accomplished by isolation of the organism in tissue culture or by detection by a nucleic acid amplification test (NAATs). Care should be taken to obtain epithelial cells, not only discharge. *C. trachomatis* can be cultured in cycloheximide-treated HeLa, McCoy, and HEp-2 cells. Chlamydia culture has been further defined by the Centers for Disease Control and Prevention (CDC) as isolation of the organism in tissue culture and as confirmation of the characteristic intracytoplasmic inclusions by staining with *C. trachomatis* species–specific fluorescein-conjugated monoclonal antibody.

NAATs are now the standard for diagnosis of *C. trachomatis* infections in adults and adolescents. These tests have high sensitivity, 10–20% greater than culture, while retaining high specificity. There are currently three Food and Drug Administration (FDA)-approved, commercially available NAATs for detection of *C. trachomatis*: polymerase chain reaction (PCR; Amplicor Chlamydia test, Roche Molecular Diagnostics, Nutley, NJ), strand displacement amplification (SDA; ProbeTec, BD Diagnostic Systems, Sparks, MD), and transcription-mediated amplification (TMA; Amp CT, Gen-Probe, San Diego, CA). PCR and SDA are DNA amplification tests that use primers that target gene sequences on the cryptogenic *C. trachomatis* plasmid that are present at approximately ten copies in each infected cell. TMA is a ribosomal RNA amplification assay. All three assays are also available as co-amplification tests for simultaneously detecting *C. trachomatis* and *Neisseria gonorrhoeae*. There are several new NAATs that are undergoing clinical trials, all using a real-time PCR platform. The currently available commercial NAATs are FDA approved for cervical swabs from adolescent and adult women, urethral swabs from adolescent and adult men, and urine from adolescent and adult men and women. TMA and SDA have also been approved for use with vaginal swabs in adolescents and adults. The vaginal swab is now the specimen of choice in females, it is better than urine equivalent to endocervical swabs, and can be self-collected. Use of urine and vaginal swabs avoids the necessity for a urethra swab or clinical pelvic examination and may greatly facilitate screening in certain populations, especially adolescents. NAATs are currently not approved for use with extragential specimens. Several recent studies suggest that NAATs are sensitive and specific for detection of *C. trachomatis* from rectal specimens in adults.

Treatment

The first line treatment regimens recommended by the CDC for uncomplicated *C. trachomatis* genital infection in men and nonpregnant women are azithromycin (1 g orally PO as a single dose) or doxycycline (100 mg PO bid for 7 days). Alternative regimens are erythromycin base (500 mg PO qid for 7 days), erythromycin ethylsuccinate (800 mg PO qid for 7 days), ofloxacin (300 mg PO bid for 7 days), and levofloxacin (500 mg PO once daily for 7 days). The high erythromycin dosages may not be well tolerated. Doxycycline and ofloxacin or levofloxacin are contraindicated in pregnant women; quinolones are contraindicated in persons younger than 18 years of age. However, use of ofloxacin and levofloxacin offer no advantages over doxycycline. For pregnant women, the recommended treatment regimen is azithromycin (1 g PO in a single dose) or amoxicillin (500 mg PO tid for 7 days). Alternative regimens are erythromycin base (250 mg PO qid for 14 days), erythromycin ethylsuccinate (800 mg PO qid for 7 days or 400 mg PO qid for 14 days).

Prognosis

Complications of genital chlamydial infections in women include perihepatitis (Fitz-Hugh-Curtis syndrome) and salpingitis. Of women with untreated chlamydial infection who develop pelvic inflammatory disease, up to 40% will have significant sequelae; approximately 17% will suffer from chronic pelvic pain, approximately 17% will become infertile, and approximately 9% will have an ectopic (tubal) pregnancy. Adolescent girls may be at higher risk for developing complications, especially salpingitis, than older women. Salpingitis in adolescent girls is also more likely to lead to tubal scarring, subsequent obstruction with secondary infertility, and increased risk for ectopic pregnancy. Women with *C. trachomatis* infection have a three- to fivefold increased risk for acquiring HIV infection.

Prevention

Timely treatment of sex partners is essential for decreasing risk for reinfection. Sex partners should be evaluated and treated if they had sexual contact during the 60 days preceding onset of symptoms in the patient. The most recent sex partner should be treated even if the last sexual contact was >60 days. Patients and their sex partners should abstain from sexual intercourse until 7 days after a single-dose azithromycin or after completion of a 7-day regimen. Annual routine screening for *C. trachomatis* is recommended for all sexually active adolescents and females 20–25 years of age, and older women with risk factors such as new or multiple partners or inconsistent use of barrier contraceptives. Sexual risk assessment may indicate more frequent screening of some women, especially adolescents.

C. trachomatis Infection in Infants

Epidemiology

Approximately 50% of neonates born to pregnant women with untreated chlamydial infection will acquire *C. trachomatis* infection. Chlamydial genital infection has been reported in 5–30% of pregnant women. The infant may become infected at one or more sites, including the conjunctivae, nasopharynx, rectum, and vagina. Transmission is rare following cesarean section with intact membranes. The introduction of systematic prenatal screening for *C. trachomatis* infection and treatment of pregnant women has resulted in a dramatic decrease in the incidence of neonatal chlamydial infection in the USA. However, in countries where prenatal screening is not done, such as the Netherlands, *C. trachomatis* remains an important cause of neonatal infection, accounting for over 60% of cases of neonatal conjunctivitis.

Clinical Manifestations

Approximately 30–50% of infants born to mothers with active, untreated, chlamydial infection develop clinical conjunctivitis. Symptoms usually develop 5–14 days after delivery, or earlier with prolonged rupture of membranes. The presentation is extremely variable and ranges from mild conjunctival injection with scant mucoid discharge to severe conjunctivitis with copious purulent discharge, chemosis, and pseudomembrane formation. The conjunctiva may be very friable and may bleed when stroked with a swab. Chlamydial conjunctivitis must be differentiated from gonococcal ophthalmia, which is sight threatening. At least 50% of infants with chlamydial conjunctivitis also have nasopharyngeal infection.

Pneumonia due to *C. trachomatis* may develop in 10–20% of infants born to women with active, untreated chlamydial infection. Only about 25% of infants with nasopharyngeal chlamydial infection develop pneumonia. *C. trachomatis* pneumonia of infancy has a very

characteristic presentation. Onset is usually from 1 to 3 months of age and is often insidious with persistent cough, tachypnea, and absence of fever. Auscultation reveals rales; wheezing is uncommon. The absence of fever and wheezing helps to distinguish *C. trachomatis* pneumonia from respiratory syncytial virus pneumonia. A distinctive laboratory finding is the presence of peripheral eosinophilia (>400 cells/mm^3). The most consistent finding on chest radiograph is hyperinflation accompanied by minimal interstitial or alveolar infiltrates.

Infants born to mothers with *C. trachomatis* may develop infection in the rectum or vagina. Although infection in these sites appears to be totally asymptomatic, it may cause confusion if identified at a later date. Perinatally acquired rectal, vaginal, and nasopharyngeal infections may persist for ≥3 years. *C. pneumoniae* can also be confused with *C. trachomatis* infection in nasopharyngeal cultures if a genus-specific monoclonal antibody is used for culture confirmation.

Diagnosis

Definitive diagnosis of *C. trachomatis* infection in infants is isolation by culture in specimens obtained from the conjunctiva or nasopharynx. Limited data suggest that NAATs may be equivalent to culture for detection of *C. trachomatis* in the conjunctiva of infants with conjunctivitis, but none of the currently available assays are approved for this indication.

Treatment

The recommended treatment regimen for *C. trachomatis* conjunctivitis or pneumonia in infants is erythromycin (base or ethylsuccinate, 50 mg/kg/day divided qid PO for 14 days). The rationale for using oral therapy for conjunctivitis is that 50% or more of these infants have concomitant nasopharyngeal infection or disease at other sites, and studies have demonstrated that topical therapy with sulfonamide drops and erythromycin ointment is not effective. The failure rate with oral erythromycin remains 10–20%, and some infants require a second course of treatment. The results of one small study suggest that a short course of azithromycin (20 mg/kg/day once daily PO for 3 days) was as effective as 14 days of erythromycin. Mothers (and their sexual contacts) of infants with *C. trachomatis* infections should be empirically treated for genital infection. An association between treatment with oral erythromycin and infantile hypertrophic pyloric stenosis has been reported in infants <6 weeks of age who were given the drug for prophylaxis after nursery exposure to pertussis.

Prevention

The most effective method of controlling perinatal chlamydial infection is screening and treatment of pregnant women. Neonatal ocular prophylaxis with topical erythromycin or tetracycline ointment, or silver nitrate, does not prevent chlamydial ophthalmia or nasopharyngeal colonization with *C. trachomatis* or chlamydial pneumonia.

Lymphogranuloma Venerum

Etiology

LGV is a systemic sexually transmitted disease caused by the L_1, L_2, and L_3 serotypes of *C. trachomatis*. Unlike the serotyopes that cause oculogenital infections, LGV strains have a predilection for lymphoid tissue. About 20 cases of LGV have been reported in children, and <1,000 cases are reported in adults in the USA annually. Recently there has been a resurgence of LGV infections, due mostly to L_2 strains, among men who have sex with men in Europe and the USA, many of these individuals were also infected with HIV.

Clinical Manifestations

The first stage of LGV is characterized by the appearance of the primary lesion, a painless, usually transient papule on the genitals. The second stage is characterized by usually unilaterally femoral or inguinal lymphadenitis with enlarging, painful buboes. The nodes may break down and drain, especially in males. In females, the vulvar lymph drains to the retroperitoneal nodes, inquinal buboes are infrequent. Fever, myalgia, and headache are common. In the tertiary stage, a genitoanorectal syndrome occurs with rectovaginal fistulas, rectal strictures, urethral destruction, and lymphedema. Among men who have sex with men, especially if they are HIV positive, rectal infection with LGV can produce a severe, acute proctocolitis, which can be confused with inflammatory bowel disease or malignancy.

Diagnosis

LGV can be diagnosed by culture of *C. trachomatis* or NAAT from a specimen aspirated from a bubo or by

serologic testing. However, NAATs will not differentiate LGV strains from the other oculogenital serotypes. Most patients with LGV will have complement-fixing antibody titers of >16.

Differential Diagnosis

Chancroid and herpes simplex virus can be distinguished clinically from LGV by the concurrent presence of painful genital ulcers. Syphilis can be differentiated by serologic tests. However, coinfections can occur.

Treatment

Doxycycline (100 mg PO bid for 21 days) is the recommended treatment. The alternative regimen is erythromycin base (500 mg PO qid for 21 days). Azithromycin (1 g PO once weekly for 3 weeks) may also be effective but clinical data are lacking. Sex partners of patients with LGV should be treated if they have had sexual contact with the patient during the 30 days preceding the onset of symptoms.

Infections due to *C. pneumoniae*

Etiology

The first isolates of *C. pneumoniae* were obtained serendipitously during trachoma studies in the 1960s (). On the basis of inclusion morphology and staining characteristics in cell culture, *C. pneumoniae* initially was considered a *C. psittaci* strain. Subsequent analysis, however, has demonstrated that this organism is distinct from both *C. psittaci* and *C. trachomatis.* Sequencing has revealed that *C. pneumoniae* differs significantly from *C. trachomatis* in several areas. *C. pneumoniae* encodes for 21 polymorphic membrane proteins (PMPs) versus 9 in *C. trachomatis.* PMPs may be surface exposed in *C. pneumoniae.* Restriction endonuclease pattern analysis, nucleic acid hybridization studies, amplified fragment length polymorphism and sequencing analysis suggest a high degree of genetic relatedness (>95%) among the *C. pneumoniae* isolates examined thus far and less than 10% homology with either *C. trachomatis* or *C. psittaci.* At this point, we do not have a strain typing system for *C. pneumoniae. C. pneumoniae* has also been isolated from nonhuman species, including horse, Australian marsupials (koalas, bandicoots), reptiles, and amphibians, where it is frequently asymptomatic but can cause respiratory infection. The animal isolates were more diverse than isolates of human origin which appear to be essentially clonal. Additional data from Australia suggests that at least two separate animal-to-human cross species transfer events may have occurred during the evolution of this organism.

Epidemiology

Respiratory infection with *C. pneumoniae* affects individuals of all ages. The proportion of community-acquired pneumonias associated with *C. pneumoniae* infection is 2–19% varying with geographic location, the age group examined, and the diagnostic methods used. Several studies of the role of *C. pneumoniae* in lower respiratory tract infection in pediatric populations have found evidence of infection from 0 to more than 18%, depending on the population and methods used. Most of these studies have relied entirely on serology for diagnosis. *C. pneumoniae* may also be responsible for 10–20% of episodes of acute chest syndrome in children with sickle cell disease, 10% of episodes of bronchitis, and 5–10% episodes of pharyngitis in children. Transmission probably occurs from person to person through respiratory droplets. Spread of the infection can occur among members in the same household or individuals in enclosed populations, such as military recruits, and in nursing homes.

Clinical Manifestations

Respiratory infections caused by *C. pneumoniae* cannot be readily differentiated from those caused by other respiratory pathogens, especially *Mycoplasma pneumoniae.* Pneumonia usually presents as a classic atypical (or nonbacterial) pneumonia characterized by mild to moderate constitutional symptoms including fever, malaise, headache, cough, and frequently pharyngitis. However, severe pneumonia with pleural effusions and empyema has been described. *C. pneumoniae* can also serve as an infectious trigger for asthma and has been isolated from middle ear aspirates of children with acute otitis media, but is usually associated with bacterial otitis media. Asymptomatic respiratory infection has been documented in 2–5% of adults and children and may persist for a year or more.

Diagnosis

It is not possible to differentiate *C. pneumoniae* from other causes of atypical pneumonia on the basis of clinical

findings. Auscultation reveals the presence of rales and often wheezing. The chest radiograph often appears worse than the patient's clinical status would indicate and may show mild, diffuse involvement or lobar infiltrates with small pleural effusions. The complete blood count may be elevated with a left shift but is usually unremarkable.

Specific diagnosis of *C. pneumoniae* infection is based on isolation of the organism in tissue culture. *C. pneumoniae* grows best in cycloheximide-treated HEp-2 and HL cells. The optimum site for culture is the posterior nasopharynx; the specimen is collected with wire-shafted swabs in the same manner as that used for *C. trachomatis*. The organism can be isolated from sputum, throat cultures, bronchoalveolar lavage fluid, and pleural fluid, but few laboratories perform such cultures because of technical difficulties. Polymerase chain reaction (PCR) testing is the most promising technology in the development of a rapid, nonculture method for detection of *C. pneumoniae*. However, no PCR assay is commercially available or has FDA approval and no PCR is standardized or has been extensively validated compared with culture for detection of *C. pneumoniae* in respiratory specimens from adults or children.

Serology is of limited utility for the diagnosis of *C. pneumoniae* infection, especially in children. Studies of *C. pneumoniae* infection in children with pneumonia and asthma show that over 50% of children with culture-documented infection have no detectable antibody using the microimmunofluorescence (MIF) assay. Acute infection, using the MIF test, has been defined as a fourfold increase in immunoglobulin G (IgG) titer or an IgM titer $\geq$16. The presence of a single elevated IgG titer $\geq$516 has been used for diagnosis of acute or chronic infection, but this has never been validated compared to culture an/or PCR and studies have shown many discrepant results. Neither an elevated IgA titer nor any other serologic marker is a valid indicator of persistent or chronic infection. The CDC has not recommended the use of any enzyme-linked immune assay for detection of antibody to *C. pneumoniae* because there is concern about the inconsistent correlation of these results with culture results. Currently there are no MIF or EIA kits that have FDA approval for serologic diagnosis of *C. pneumoniae* infection.

Treatment

The optimum dose and duration of antimicrobial therapy for *C. pneumoniae* infections remain uncertain. As most published treatment studies have used serology only for diagnosis, microbiologic efficacy could not be assessed. Recrudescent symptoms and persistent positive cultures have been described following 2 weeks of erythromycin and 30 days of tetracycline or doxycycline. Tetracyclines, erythromycin, azithromycin, clarithromycin, and quinolones have good in vitro activity against *C. pneumoniae*. *C. pneumoniae* is constitutively resistant to sulfonamides. The results of several treatment studies that have utilized culture have shown that erythromycin (40 mg/kg/day divided bid PO for 10 days), clarithromycin (15 mg/kg/day divided bid PO for 10 days), and azithromycin (10 mg/kg PO on day 1, then 5 mg/kg/day PO on days 2–5) are effective for eradication of *C. pneumoniae* from the nasopharynx of children with pneumonia in approximately 80% of cases. Persistence is not due to the development of resistance as MICs of the isolates obtained before and after therapy were unchanged.

Infections due to *C. psittaci*

Etiology

C. psittaci, the agent of psittacosis (also known as parrot fever and ornithosis), is primarily an avian pathogen and causes human disease infrequently. *C. psittaci* affects psittacine birds (parrots, parakeets, macaws, etc.) and nonpsittacine birds as well (ducks, turkeys); the known host range includes 130 avian species. Strains of *C. psittaci* have been analyzed by patterns of pathogenicity, inclusion morphology in tissue culture, DNA restriction endonuclease analysis, and monoclonal antibodies, which indicate that there are seven avian serovars. Two of the avian serovars, psittacine and turkey, are of major importance in the avian population of the USA. Each is associated with important host preferences and disease characteristics.

Epidemiology

From 2001 to 2008, there were 128 reported cases of psittacosis in the USA. Of these, 85% were associated with exposure to birds, including 70% following exposure to caged pet birds, which were usually psittacine birds including cockatiels, parakeets, parrots, and macaws. Chlamydiosis among caged nonpsittacine birds occurs most frequently in pigeons, doves, and mynah birds. Persons at highest risk for acquiring psittacosis include bird fanciers and owners of pet birds (43% of cases) and pet shop employees (10% of cases). There have also been large

outbreaks associated with poultry processing (turkeys, ducks). Reported cases most likely underestimate the number of actual infections due to a lack of awareness.

Inhalation of aerosols from feces, fecal dust, and nasal secretions of animals infected with *C. psittaci* is the primary route of infection. Source birds are either asymptomatic or have anorexia, ruffled feathers, lethargy, and watery green droppings. Psittacosis is uncommon in children, in part because children may be less likely to have close contact with infected birds. One high-risk activity is cleaning the cage. Several major outbreaks of psittacosis have occurred in turkey processing plants; workers exposed to turkey viscera are at the highest risk for infection.

Clinical Manifestations

Infection with *C. psittaci* in humans ranges from clinically inapparent to severe infection involving multiple organ systems as well as pneumonia. The mean incubation period is 15 days after exposure, with a range of 5–21 days. Onset of disease is usually abrupt, with fever, cough, headache, and malaise. The fever is high and often is associated with rigors and sweats. The headache can be so severe that meningitis is considered. The cough is usually nonproductive. Gastointestinal symptoms are occasionally reported. Crackles may be heard on auscultation. Chest radiographs are usually abnormal with variable infiltrates, and pleural effusions may be present. The white blood cell count is usually not elevated, but a mild leukocytosis may be present. Elevated levels of aspartate aminotransferase, alkaline phosphatase, and bilirubin are common.

Diagnosis

The diagnosis of psittacosis can be difficult because of the varying clinical presentations. A history of exposure to birds or association with an active case are important clues, but as many as 20% of patients with psittacosis have no known contact. Person-to-person spread has been suggested but not proved. Other infections that cause pneumonia with high fever, unusually severe headache, and myalgia include, most commonly, bacterial and viral respiratory infections as well as *Coxiella burnetii* (Q fever), *Mycoplasma pneumoniae, C. pneumoniae,* tularemia, tuberculosis, fungal infections, and Legionnaires disease.

The 2010 CDC case definition of psittacosis requires a compatible clinical illness, usually with a reliable history of avian exposure with laboratory confirmation by one of the following four methods: (1) culture of *C. psittaci* from respiratory specimens (e.g., sputum, pleural fluid or tissue) or blood, (2) a fourfold or greater increase in CF or MIF titer in sera collected at least 2–4 weeks apart, (3) supportive serology (e.g., *C. psittaci* IgM titer of $\geq$32 in at least one serum sample obtained at onset of symptoms), or (4) detection of *C. psittaci* DNA in a respiratory specimen (e.g., sputum, pleural fluid or tissue) via amplification of a specific target by PCR. A probable case: An illness characterized by fever, chills, headache, cough, and myalgia that has either (1) supportive serology (e.g., *C. psittaci* IgM titer of $\geq$32 in at least one serum sample obtained at onset of symptoms) or (2) detection of *C. psittaci* DNA in a respiratory specimen (e.g., sputum, pleural fluid or tissue) via amplification of a specific target by PCR. A confirmed case would be a patient with the above clinical presentation with either (1) culture of *C. psittaci* from respiratory specimens (e.g., sputum, pleural fluid or tissue) or blood or (2) a fourfold or greater increase in complement fixation (CF) or MIF titer in sera collected at least 2–4 weeks apart. Although MIF has shown greater specificity for *C. psittaci* than CF, cross reactions with other *Chlamydia* species and bacteria can occur. To increase the reliability of the test results, acute and convalescent phase serum specimens should be analyzed in the same laboratory at the same time. Early treatment of psittacosis with tetracycline may abrogate the antibody response.

Although *C. psittaci* will grow in the same culture systems used for isolation of *C. trachomatis* and *C. pneumoniae,* very few laboratories culture for *C. psittaci,* mainly because of the potential biohazard (Table 78.2). PCR assays for detection of *C. psittaci* have been reported in the literature, but there are no FDA approved, commercially available kits for the diagnosis of infection in humans.

Treatment

Recommended treatment regimens for psittacosis are doxycycline (100 mg PO bid) or tetracycline (500 mg PO qid) for at least 10–14 days after the fever abates. The initial treatment of severely ill patients is doxycycline hyclate (4.4 mg/kg/day divided every 12 h IV, maximum 100 mg/dose). Erythromycin (500 mg qid PO) or azithromycin (10 mg/kg PO day 1, not to exceed 500 mg, followed by 5 mg/kg PO on days 2–5, not to exceed 250 mg) are alternative drugs if tetracyclines are contraindicated (e.g., children <8 years of age and pregnant women), but may be less effective. Remission is usually evident within 48–72 h. Initial infection does not appear to be followed by long-term immunity. Reinfection

Table 78.2
Laboratories that test human specimens for *Chlamydophila psittaci*

Laboratory	Tests performed	Telephone number web site
Focus Diagnostics Inc. (Quest subsidiary), Cypress, CA	Culture, MIF (IgM, IgA, IgG)	(800) 445-4032 www.focusdx.com
Laboratory Corporation of America, Burlington, NC	Culture, MIF (IgM, IgG)	(800) 222-7566 www.labcorp.com
Specialty Laboratories, Santa Monica, CA	MIF (IgM, IgG, IgA)	(800) 421-4449 www.specialtylabs.com
ViroMed Laboratories Minnetonka, MN	Culture, MIF (IgG, IgM)	(800) 582-0077 www.viromed.com
Response and Surveillance Laboratory, Respiratory Diseases Branch, CDC Atlanta, GA[a]	MIF (requires paired sera), PCR, culture, genotyping (multiple specimen types)	(404) 639-4921

Source: National Association of State Public Health Veterinarians (NASPV) (2010) Compendium of measures to control *Chlamydophila psittaci* infections among humans (psittacosis) and pet birds (avian chlamydiosis) http://www.nasphv.org/documentsCompendiaPsittacosis.html
MIF, microimmunofluorescence; PCR, polymerase chain reaction
[a]CDC is a reference laboratory and samples must be submitted through State Health Departments

and clinical disease can develop within 2 months of treatment; only two well-documented cases of reinfection have been reported in the literature.

Prognosis

The mortality rate of untreated psittacosis is 15–20%, but is <1% with appropriate treatment. Severe illness leading to respiratory failure and fetal death has been reported among pregnant women.

Prevention

Several control measures are recommended to prevent transmission of *C. psittaci* from birds. Bird fanciers should be cognizant of the potential risk. *C. psittaci* is susceptible to most disinfectants and detergents as well as heat, but is resistant to acid and alkali. Accurate records of all bird-related transactions aid in identifying sources of infected birds and potentially exposed persons. Newly acquired birds, including birds that have been to shows, exhibitions, fairs, or other events, should be isolated for 30–45 days or tested or treated prophylactically before adding them to a group of birds. Care should be taken to prevent transfer of fecal material, feathers, food, or other materials between birdcages. Birds with signs of avian chlamydiosis (e.g., ocular or nasal discharge, watery green droppings, or low body weight) should be isolated and should neither be sold nor purchased. Their handlers should wear protective clothing and a disposable surgical cap and use a respirator with an N95 or higher efficiency rating (not a surgical mask) when handling them or cleaning their cages. Infected birds should be isolated until fully treated, which is generally 45 days.

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