Chlamydia trachomatis and Chlamydia pneumoniae Infections in Children and Adolescents

Margaret R. Hammerschlag

Pediatrics in Review 2004;25;43
DOI: 10.1542/pir.25-2-43

Chlamydia trachomatis and *Chlamydia pneumoniae* Infections in Children and Adolescents

Margaret R. Hammerschlag, MD*

Objectives

After completing this article, readers should be able to:

1. Discuss the spectrum and clinical manifestations of diseases caused by *Chlamydia trachomatis* in different age groups.
2. Delineate the appropriate use of nonculture tests for diagnosis of *C trachomatis* infection in infants, children, and adolescents and the consequences of inappropriate use of these tests.
3. Characterize the appropriate treatments for *C trachomatis* infection in infants, children, and adolescents.
4. Describe the epidemiology, spectrum, and clinical manifestations of diseases caused by *C pneumoniae*.
5. Discuss the limitations of serology in the diagnosis of *C pneumoniae* infections in children.
6. Describe appropriate treatment of *C pneumoniae* infections.

Introduction

Chlamydiae are obligate intracellular pathogens that have established a unique niche within the host cell. The order contains one genus, *Chlamydia*, with four recognized species: *C trachomatis, C psittaci, C pneumoniae*, and *C pecorum*. Of these, *C trachomatis* and *C pneumoniae* are significant human pathogens. *C psittaci* is an important cause of zoonosis. However, based on the results of recent taxonomic analysis using the 16S and 23S rRNA genes, this classification is being revised. The new analysis has suggested splitting the genus *Chlamydia* into two genera, *Chlamydia* and *Chlamydophila*. Two new species, *Chlamydia muridarum* (formerly the agent of mouse pneumonitis) and *C suis*, would join *C trachomatis*. *Chlamydophila* would contain *C pecorum, C pneumoniae,* and *C psittaci* as well as three new species split off from *C psittaci*: *C abortus*, *C caviae* (formerly *C psittaci* guinea pig conjunctivitis strain), and *C felis*. Controversy continues regarding this reclassification, but for the purposes of this review, we will continue to refer to *Chlamydia*.

Chlamydiae are characterized by a unique developmental cycle that has morphologically distinct infectious and reproductive forms: elementary body (EB) and reticulate body (RB). Chlamydiae also share a group-specific lipopolysaccharide antigen and use host adenosine triphosphate (ATP) for the synthesis of chlamydial protein. Although chlamydiae use the host cell's pool for three of four nucleoside triphosphates, they do encode functional glucose-catabolizing enzymes, which can be used for generation of ATP. For some reason, however, these genes are "turned off." All chlamydiae also encode an abundant protein called the major outer membrane protein (MOMP or OmpA) that is surface-exposed in *C trachomatis* and *C psittaci*, but apparently not in *C pneumoniae*. The MOMP is the major determinant of the serologic classification of *C trachomatis* and *C psittaci* isolates.

Understanding the life cycle of chlamydiae is important because it underlies the potential problems with diagnosis and treatment. As shown in the Figure, following infection, the infectious EBs, which are 200 to 400 mcm in diameter, attach to the host cell by a process of electrostatic binding and are taken into the cell by endocytosis, which does

*Department of Pediatrics, Division of Infectious Diseases, State University of New York Downstate Medical Center, Brooklyn, New York.

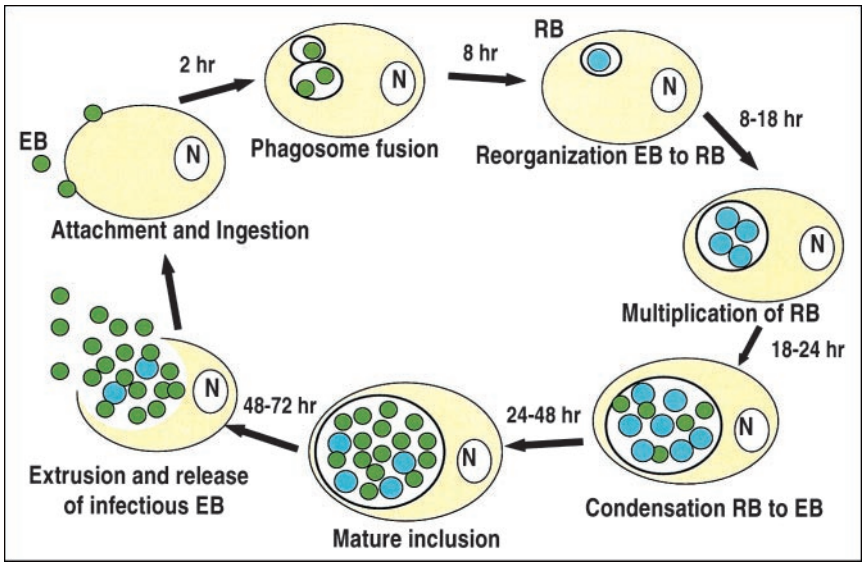

Figure. Life cycle of chlamydiae in epithelial cells. N=nucleus, EB=elementary body, RB=reticulate body.

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 EBs then differentiate into RBs that undergo binary fission; after approximately 36 hours, the RBs differentiate back into EBs, and infectivity increases. At about 48 hours, release may occur by cytolysis or by a process of exocytosis or extrusion of the entire inclusion, leaving the host cell intact. Unlike other bacteria, the life cycle of chlamydiae is prolonged (48 to 72 hr versus 20 min). Thus, treatment requires multiple-dose regimens for 5 to 14 days, depending on the species and site of infection. Single-dose azithromycin treats genital *C trachomatis* infection effectively because it has a half-life in tissue of 5 to 7 days. However, single-dose azithromycin does not eradicate *C pneumoniae* from the respiratory tract. The ability to cause prolonged, often subclinical infection is one of the major characteristics of chlamydiae.

Infection Due to *C trachomatis* in Children and Adolescents

Epidemiology

C trachomatis infection is the most prevalent sexually transmitted infection and infectious disease in the United States today. The Centers for Disease Control and Prevention (CDC) estimates that the number of new *C trachomatis* infections exceeds 4 million annually. The prevalence of *C trachomatis* infection is consistently greater than 5% among sexually active adolescent and young adult women attending outpatient clinics, regardless of the region of the country, location of the clinic (urban or rural), or race or ethnicity of the population. Among sexually active adolescents, the prevalence commonly exceeds 10% and may exceed 20%. Reinfection appears to be frequent. Infection with *C trachomatis* tends to be asymptomatic and of long duration. If a pregnant woman has active infection during delivery, the infant may acquire the infection, developing either conjunctivitis or pneumonia. Rarely, children also may acquire chlamydial infection as a result of sexual abuse.

Infections in Infants

Pregnant women who have cervical *C trachomatis* infection can transmit the infection to their infants, who subsequently may develop neonatal conjunctivitis and pneumonia. Epidemiologic evidence strongly suggests that the infant acquires chlamydial infection from the mother during vaginal delivery. Infection after cesarean section is rare and usually occurs after early rupture of the amniotic membrane. No evidence supports postnatal acquisition from the mother or other family members. Approximately 50% to 75% of infants born to infected women become infected at one or more anatomic sites, including the conjunctiva, nasopharynx, rectum, and vagina. However, the epidemiology of perinatal *C trachomatis* infection has changed over the past decade. The introduction of highly sensitive and specific nucleic acid amplification tests (NAATs) for detection of *C trachomatis* coupled with systematic screening and treatment of chlamydial infection in pregnant women have resulted in

a marked decrease in perinatally acquired *C trachomatis* infection.

Approximately 30% to 50% of infants born to *Chlamydia*-positive mothers develop conjunctivitis. Studies in the 1980s identified *C trachomatis* in 14% to 46% of infants younger than 1 month of age presenting with conjunctivitis. As stated previously, chlamydial ophthalmia appears to occur much less frequently now because of systematic screening and treatment of pregnant women. The incubation period for chlamydial conjunctivitis is 5 to 14 days after delivery or earlier if membranes have ruptured prematurely. At least 50% of affected infants also have nasopharyngeal infection. The presentation varies, ranging from mild conjunctival injection with scant mucoid discharge to severe conjunctivitis with copious purulent discharge, chemosis, and pseudomembrane formation. The conjunctiva can be friable and may bleed when stroked with a swab. Chlamydial conjunctivitis must be differentiated from gonococcal ophthalmia in some infants, especially those born to mothers who did not receive any prenatal care, had gonorrhea during pregnancy, or abused drugs. Overlap in both incubation periods and presentation is possible.

Approximately 70% of infants who have perinatal chlamydial infection are infected in the nasopharynx. However, most of these infections are asymptomatic and may persist for 3 years or more. Only about 30% of infants who have nasopharyngeal infection develop pneumonia. Infants who have *C trachomatis* pneumonia usually present between 4 and 12 weeks of age. A few cases have been reported presenting as early as 2 weeks of age, but no cases have been seen beyond 4 months of age. The infants frequently have a history of cough and congestion with an absence of fever. On physical examination, the infant exhibits tachypnea, and rales are heard on auscultation of the chest; wheezing is distinctly uncommon. There are no specific radiographic findings except hyperinflation. Lobar consolidation and pleural effusions are not seen. Significant laboratory findings include peripheral eosinophilia (>300/mcL [0.3 x 10^9/L]) and elevated serum immunoglobulin concentrations.

Infants born to *Chlamydia*-positive mothers also may become infected in the rectum and vagina. Although infection at these sites appears to be asymptomatic, the infection may cause confusion with possible sexual acquisition if detected later.

Infections in Older Children

C trachomatis has not been associated with specific clinical syndromes among older infants and children. Most attention to *C trachomatis* infection in this age group has concentrated on the relationship to sexual abuse. It has been suggested that the isolation of *C trachomatis* from a rectal or genital site in children who have not had prior sexual activity may be a marker of sexual abuse, although evidence for other modes of spread, such as through fomites, is lacking for this organism. Perinatal maternal-infant transmission resulting in vaginal or rectal infection has been documented, with prolonged infection for up to 3 years. This represents an important confounding variable. Most studies have documented rectogenital chlamydial infection in 2% to 3% of sexually abused children when these children were cultured routinely for the organism. Most infected children were asymptomatic. In the setting of repeated abuse by a family member over long periods, development of infection would be difficult to demonstrate. The 2002 Sexually Transmitted Diseases Treatment Guidelines from the CDC do not recommend routine pharyngeal and urethral cultures for *C trachomatis* among children who are suspected victims of sexual abuse. The primary reasons for this recommendation were the low yield from the urethra, the tendency for longer persistence of perinatally acquired pharyngeal infection, and the potential confusion with *C pneumoniae* infection.

Infections in Adolescents

C trachomatis causes a spectrum of disease in sexually active adolescents and adults. Rates of infection among adolescent girls exceed 20% in many urban populations, but can be as high as 15% in suburban populations, as well. One study of sexually active adolescent girls found that almost 40% became reinfected within 9 months. The new infections were usually the same serotype as the index infection, suggesting either persistence or reacquisition from an untreated partner. *C trachomatis* causes 23% to 55% of all cases of nongonococcal urethritis in men, although the proportion of chlamydial nongonococcal urethritis has been declining gradually. As many as 50% of men who have gonorrhea may be coinfected with *C trachomatis.*

In women, *C trachomatis* infects the transitional epithelium of the endocervix. *C trachomatis* infection occurs more frequently in females who have ectopy, which is more common in adolescents. Ectopic cervical cells are more susceptible than cornified epithelium to *C trachomatis* infection. *C trachomatis* can cause mucopurulent cervicitis, which is characterized by the presence of a mucopurulent cervical discharge. However, 70% or more of endocervical infections in women are asymptomatic. It is not possible to diagnose chlamydial infection accurately based solely on the physical examination because

most examination results are normal. Women also may develop urethritis due to *C trachomatis* infection, which is characterized by sterile pyuria. Other manifestations of *C trachomatis* infection in females include bartholinitis, endometritis, salpingitis (which may be subclinical in adolescents), and perihepatitis (Fitz-Hugh–Curtis syndrome). Salpingitis due to *C trachomatis* is more likely to result in tubal obstruction, subsequent infertility, and increased risk of ectopic pregnancy than is disease due to *Neisseria gonorrhoeae* or Gram-negative enteric organisms. Perihepatitis should be suspected in young, sexually active women who present with right upper quadrant pain, fever, nausea, or vomiting. Many patients who have perihepatitis due to *C trachomatis* also have evidence of salpingitis.

C trachomatis infection in males is characterized primarily by urethritis, although chlamydial urethritis cannot be differentiated readily from chlamydia-negative urethritis on the basis of signs or symptoms. The incubation period is usually 7 to 14 days compared with 3 to 5 days for gonorrhea. Patients present with dysuria and moderate whitish or clear urethral discharge. Urethritis in males often is subclinical or asymptomatic and may be detected only by the presence of microscopic pyuria in a first-void urine sample. *C trachomatis* also is the most frequent cause of epididymitis in sexually active young men. Clinically, epididymitis presents with unilateral scrotal pain, swelling, tenderness, and fever in a young man who has chlamydial urethritis. However, the urethritis may be asymptomatic, as described previously. Other conditions associated with *C trachomatis* infection in males include proctitis, prostatitis, and Reiter syndrome.

Diagnosis

The "gold standard" for diagnosing *C trachomatis* infections in infants and children remains isolation by culture of the pathogen from the conjunctiva, nasopharynx, vagina, or rectum. *Chlamydia* culture has been defined further by the CDC as isolation of the organism in tissue culture and confirmation by microscopic identification of the characteristic inclusions by fluorescent antibody staining. Several nonculture methods have received United States Food and Drug Administration (FDA) approval for diagnosis of chlamydial conjunctivitis. These include enzyme immunoassays (EIAs), specifically Chlamydiazyme (Abbott Diagnostics, Chicago, IL) and MicroTrak EIA (Genetic Systems, Seattle, WA), and direct fluorescent antibody tests (DFAs), including Syva MicroTrak (Genetic Systems, Seattle, WA) and Pathfinder (Sanofi-Pasteur, Chaska, MN). These tests appear

Table. Relative Limits of Detection of Different Assays for *C trachomatis*

Test	Number of Organisms/Sample[a]
Amplified DNA/RNA	1 to 10^1
Culture	10^1 to 10^2
DFA[b]	10^1 to 10^3
DNA Probe	10^3 to 10^4
EIA[c]	10^3 to 10^5

[a]Log number of chlamydial elementary bodies
[b]Direct fluorescent antibody test
[c]Enzyme immunoassay

to perform well with conjunctival specimens; they have sensitivities of at least 90% and specificities of at least 95% compared with culture. Unfortunately, the performance of these tests with nasopharyngeal specimens has not been as good; sensitivities range from 33% to more than 90%. The commercially available DNA probe, Pace II (GenProbe, San Diego, CA), has FDA approval only for cervical and urethral sites in adults, in whom its performance has been similar to that of most of the approved EIAs available. It does not have approval for any site in children. The DNA probe is not an amplification test.

A major advance in the diagnosis of *C trachomatis* infection during the past decade has been the introduction of NAATs, which have high sensitivity, perhaps even detecting 10% to 20% more cases than culture, while retaining high specificity. As shown in the Table, the relative limits of detection of *C trachomatis* range from approximately 10^3 to 10^5 organisms per clinical sample using an EIA or DNA probe to 1 to 10^1 organisms with an NAAT. There currently are three FDA-approved, commercially available NAATs for diagnosis of *C trachomatis* infection: 1) polymerase chain reaction (PCR) [Amplicor (Roche Molecular Diagnostics, Nutley, NJ)], 2) strand displacement amplification (SDA) [ProbeTec (Becton Dickson, Sparks, MD)], and 3) transcription-mediated amplification (TMA) [GenProbe (San Diego, CA)]. A fourth assay, ligase chain reaction (LCR) [LCx *Chlamydia trachomatis* Assay (Abbott Diagnostics, Abbott Park, IL)], was withdrawn from the market in 2003. The first two available tests are DNA amplification methods; the last is an RNA amplification test. All of the assays have received FDA approval for cervical swabs from women, urethral swabs from men, and urine from men and women. These tests also have performed very well in adolescents. The use of noninvasive specimens such as

urine is especially helpful in high-prevalence populations such as sexually active adolescents. Data on the use of NAATs in children are limited. Preliminary data suggest that PCR is equivalent to culture for detecting *C trachomatis* in the conjunctiva and nasopharynx of infants who have conjunctivitis.

Nonculture tests never should be used for rectal or vaginal sites in children or for any forensic purposes in adolescents or adults. Only culture should be used in these circumstances. Isolation of the organism in tissue culture should be confirmed by microscopic identification of the inclusions by staining with a fluorescein conjugated *C trachomatis* species-specific monoclonal antibody. EIAs are not acceptable for culture confirmation; their use has led to false-positive reports. Isolates of *C trachomatis* should be preserved. Use of nonculture tests for detection of *C trachomatis* vaginal and rectal specimens has been associated with a large number of false-positive results. Fecal material can give false-positive reactions with any EIA; none is approved for this site in adults. Common bowel organisms, including *Escherichia coli*, *Proteus* sp, vaginal organisms (eg, group B *Streptococcus* and *Gardnerella vaginalis*), and even some respiratory tract flora (eg, group A *Streptococcus*) also can give positive reactions with EIAs. These types of tests are best for screening for genital infection in adolescents and adults in high-prevalence populations (prevalence of infection >7%). Because all of the available EIAs use genus-specific antibodies, if they are used for respiratory tract specimens, they also will detect *C pneumoniae*. NAATs also are not approved for detection of *C trachomatis* in rectogenital sites from prepubertal children and rectal specimens in adults. The major problem with rectal specimens is the presence of inhibitors of DNA polymerase, which can lead to false-negative results. Data on the use of NAATs for vaginal specimens or urine from children are very limited and insufficient to allow a recommendation on their use. The CDC suggests that NAATs be used as an alternative to culture *only* if confirmation is available, which means using a second FDA-approved NAAT that targets a different gene sequence from the initial test.

The "gold standard" for diagnosing *C trachomatis* infections in infants and children remains isolation by culture of the pathogen from the conjunctiva, nasopharynx, vagina, or rectum.

Prevention and Control

Because *C trachomatis* infections are transmitted vertically from mother to infant during delivery, there are several possible options for intervention. One of the first to be considered was neonatal ocular prophylaxis. However, several large studies in the United States have demonstrated that ocular prophylaxis with either erythromycin or tetracycline ophthalmic ointments are not effective in preventing chlamydial ophthalmia. Neonatal ocular prophylaxis should be directed primarily toward preventing gonococcal ophthalmia because it is the pathogen that poses the greatest risk of eye injury. The most effective method for controlling perinatal chlamydial infection is screening and treatment of pregnant women. The CDC currently recommends either amoxicillin or erythromycin base as first-line regimens for treating *C trachomatis* infection in pregnant women. Single-dose azithromycin is listed as an alternative regimen with the caveat that data on its use are insufficient to recommend routine use in pregnant women. However, clinical experience and preliminary data suggest that azithromycin is safe and effective. Reasons for failure of maternal treatment to prevent infantile chlamydial infection include poor compliance and reinfection from an untreated sexual partner. Even with effective screening, some infected women will be missed, depending on the diagnostic methods used. Another consideration is women who do not seek prenatal care.

Treatment

C trachomatis is susceptible to antibiotics that interfere with protein or DNA synthesis, including macrolides, tetracyclines, quinolones, and sulfonamides. Although the in vitro activities of beta-lactam antibiotics vary, chlamydiae have penicillin-binding proteins, and amoxicillin has been found to be effective in treating *C trachomatis* infections in pregnant women. Oral erythromycin suspension (ethylsuccinate or stearate 50 mg/kg per day for 10 to 14 d) is the therapy of choice for treating chlamydial conjunctivitis and pneumonia in infants. It provides better and faster resolution of the conjunctivitis and treats any concurrent nasopharyngeal infection,

which prevents the development of pneumonia. Additional topical therapy is not needed. The efficacy of this regimen has been reported as 80% to 90%; as many as 20% of infants may require another course of therapy. Erythromycin at the same dose for 2 to 3 weeks is the treatment of choice for pneumonia; it results in both clinical improvement and elimination of the organism from the respiratory tract. An association between treatment with oral erythromycin and infantile hypertrophic pyloric stenosis has been reported in infants younger than 6 weeks of age who received the drug for prophylaxis after exposure to pertussis in the nursery. Data on the use of other macrolides (azithromycin or clarithromycin) to treat neonatal chlamydial infection are limited. The results of one small study suggested that a short course of azithromycin 20 mg/kg per day orally (one dose daily for 3 days) was as effective as 2 weeks of erythromycin.

Chlamydial infections in older children may be treated with oral erythromycin (50 mg/kg per day qid to a maximum of 2 g/d for 7 to 14 d). Children older than 8 years of age may be treated with tetracycline (25 to 50 mg/kg per day qid orally for 7 d). A single 1-g oral dose of azithromycin may be used in children who weigh at least 45 kg or are at least 8 years of age. The first-line treatment for uncomplicated *C trachomatis* infections in adults and adolescents is a single 1-g dose of azithromycin or doxycycline 100 mg bid administered orally for 7 days. Alternative regimens include oral erythromycin base (500 mg) or oral erythromycin ethylsuccinate (800 mg) qid for 7 days, oral ofloxacin 300 mg bid for 7 days, or oral levofloxacin 500 mg once a day for 7 days.

Infection Due to *C pneumoniae* in Children and Adolescents

The Organism

On the basis of inclusion morphology and staining characteristics in cell culture, *C pneumoniae* initially was considered a *C psittaci* strain. Subsequent analyses, however, have demonstrated that this organism is distinct from both *C psittaci* and *C trachomatis.* Restriction endonuclease pattern analysis, nucleic acid hybridization studies, and amplified fragment length polymorphism analysis suggest a high degree of genetic relatedness (>95%) among the *C pneumoniae* isolates examined so far and less than 10% homology with either *C trachomatis* or *C psittaci.* At this point, there is no strain typing system for *C pneumoniae.*

Epidemiology

C pneumoniae appears to be a common human respiratory pathogen, infecting all ages over a wide geographic distribution. The organism also has been isolated from nonhuman species, including a horse, koalas, reptiles, and amphibians, although the potential role of these infections in human disease is unknown. The mode of transmission remains uncertain, but it probably involves infected respiratory tract secretions. Several studies of the role of *C pneumoniae* in lower respiratory tract infection in pediatric populations have found evidence of infection in 0% to more than 18%, depending on the population studied and the methods used. Studies that have used culture have found a poor correlation between culture and serology, especially among children. Asymptomatic nasopharyngeal carriage occurs in 2% to 5% of adults and children. It is not known what role asymptomatic carriage plays in the epidemiology of *C pneumoniae*, but it is possible that affected persons may represent a reservoir for spread of infection.

Clinical Presentation

Initial reports of *C pneumoniae* infection emphasized mild atypical pneumonia that clinically resembled that associated with *Mycoplasma pneumoniae.* In several subsequent studies, pneumonia associated with *C pneumoniae* has been clinically indistinguishable from other pneumonias. Coinfection with other pathogens, especially *M pneumoniae* and *S pneumoniae,* can be frequent. In one multicenter pneumonia treatment study, 20% of children who had positive *C pneumoniae* cultures were coinfected with *M pneumoniae*, and they could not be distinguished clinically from children who were infected with either organism alone. *C pneumoniae* has been associated with severe illness and even death, although the contribution of pre-existing chronic conditions in many of these patients is difficult to assess. In some cases, *C pneumoniae* clearly is implicated as a serious pathogen, even in the absence of underlying disease. For example, *C pneumoniae* was isolated from the respiratory tract and the pleural fluid of a previously healthy adolescent boy who had severe pneumonia complicated by respiratory tract failure and pleural effusions.

The role of *C pneumoniae* in upper respiratory tract infections is less well defined. The pathogen has been isolated from middle ear fluids in approximately 8% of children who had acute otitis media. However, most of these patients were coinfected with other bacteria. Symptoms suggestive of sinus involvement are common among patients who have upper respiratory tract infection associated with *C pneumoniae*, but there is only one report of the isolation of the organism from a 47-year-old man who had sinusitis. Data also are limited on the potential role of *C pneumoniae* in pharyngitis. There are

only two published studies, and the diagnosis was limited to serology.

Diagnosis

C pneumoniae infection can be diagnosed specifically by isolation of the organism from nasopharyngeal or throat swabs, sputa, or pleural fluid, if present. The nasopharynx appears to be the optimal site for isolation of the organism. *C pneumoniae* grows readily in cell lines derived from respiratory tract tissue, specifically HEp-2 and HL cells. Nasopharyngeal cultures can be obtained with Dacron®-tipped, wire-shafted swabs. Each lot of swabs should be treated in a mock-infection system to ensure a lack of inhibitory effects on either viability of cells or recovery of chlamydia. Specimens for culture should be placed in appropriate transport media, usually a sucrose-phosphate buffer with antibiotics and fetal calf serum, and stored immediately at 4°C for no longer than 24 hours. Viability decreases if specimens are held at room temperature. If the specimen cannot be processed within 24 hours, it should be frozen at −70°C until culture can be performed. After 72 hours of incubation, culture can be confirmed by staining with either a *C pneumoniae* species-specific or a *Chlamydia* genus-specific (anti-lipopolysaccharide) fluorescein conjugated monoclonal antibody. Inclusions of *C pneumoniae* do not contain glycogen and, thus, do not stain with iodine. Unfortunately, the availability of commercially produced *C pneumoniae*-specific reagents is limited. If a genus-specific antibody is used, the presence of *C pneumoniae* should be confirmed by differential staining with a specific *C trachomatis* antibody; if the latter is negative, the isolate is either *C pneumoniae* or *C psittaci*. If there is no avian exposure, psittacosis is highly unlikely.

Although serology using the microimmunofluorescence (MIF) test has been employed most frequently to diagnose *C pneumoniae* infection, acute, culture-documented infection also can occur without seroconversion, especially in children. The original criteria, as proposed by Grayston and associates in the early 1990s, considered a fourfold rise in immunoglobulin (Ig) G or a single IgG titer of at least 1:512 or a single IgM titer of at least 1:16 to be indicative of acute infection. Although 7% to 13% of children, 6 months to 16 years of age enrolled in two multicenter pneumonia treatment studies, were culture-positive, and 7% to 18% met the serologic criteria with the MIF test for acute infection, they were not the same patients. Only 1% to 3% of the culture-positive children met the serologic criteria; approximately 70% were seronegative. Most had no detectable antibody by the MIF test, even after 3 months of follow-up. However, these children did have antibody to a number of *C pneumoniae* proteins when their sera were examined by immunoblotting, but not to the MOMP, which is probably the major antigen presented in the MIF test. Unfortunately, it was not possible to differentiate culture-positive from culture-negative children, even with immunoblotting. This should not be entirely surprising because serology also is of very limited value in diagnosing *C trachomatis* genital infection. In addition, the MIF test is not standardized, and there is significant interlaboratory variation. The CDC recently proposed modifications of the serologic criteria for diagnosing *C pneumoniae* infection. Although the MIF test was considered to be the only currently acceptable serologic test, the criteria were made significantly more stringent. Acute infection, using the MIF, was defined as a fourfold rise in IgG or an IgM titer of at least 1:16; use of a single elevated IgG titer was discouraged. An IgG of 1:16 or greater was believed to indicate past exposure. At best, serology only offers a retrospective diagnosis because acute and convalescent sera must be obtained.

C pneumoniae infection can be diagnosed specifically by isolation of the organism from nasopharyngeal or throat swabs, sputa, or pleural fluid, if present.

Although at least 18 in-house PCR assays for detection of *C pneumoniae* in clinical specimens have been reported in the literature, none is standardized or has been validated extensively compared with culture for detection of *C pneumoniae* in respiratory specimens. None is commercially available or has FDA approval. Recent studies also suggest significant inter- and intra-laboratory variation in the performance of PCR for *C pneumoniae*. The CDC did not recommend any specific assay, citing the lack of comparative data, and suggested the need for more studies that had proper controls and larger numbers of clinical specimens from patients.

Unfortunately, most clinicians will not be able to make a specific microbiologic diagnosis of *C pneumoniae* infection. This may change when and if a validated,

FDA-approved PCR kit becomes commercially available. In the interim, the clinician should think syndromically. If atypical pneumonia is suspected based on epidemiologic and clinical findings, using or adding a macrolide antibiotic may be considered.

Treatment

C pneumoniae, like *C trachomatis*, is susceptible to macrolides, tetracyclines, and quinolones, but unlike *C trachomatis*, it is resistant to sulfonamides. To date, few published data have described the response of *C pneumoniae* to antimicrobial therapy. Most treatment studies of pneumonia caused by *C pneumoniae* published to date have relied solely on serologic diagnosis. Thus, microbiologic efficacy could not be assessed. Anecdotal reports have suggested that prolonged courses (up to 3 weeks) of either tetracyclines or erythromycin may be needed to eradicate *C pneumoniae* from the nasopharynx of adults who have flulike illness and pharyngitis. Results of two pediatric multicenter pneumonia treatment studies found that 10-day courses of erythromycin and clarithromycin and 5 days of azithromycin suspension were equally efficacious, eradicating the organism in 79% to 86% of children. Quinolones, including levofloxacin and moxifloxacin, also have demonstrated 70% to 80% efficacy in eradicating *C pneumoniae* from adults who had community-acquired pneumonia. Most patients improved clinically despite persistence of the organism. Persistence does not appear to be due to the development of antibiotic resistance.

Based on these limited data, the following regimens for respiratory tract infection due to *C pneumoniae* can be suggested. For adolescents: doxycycline 100 mg bid for 14 to 21 days, tetracycline 250 mg qid for 14 to 21 days, azithromycin 1.5 g for 5 days, levofloxacin 500 mg/d orally or intravenously for 7 to 14 days, or moxifloxacin 400 mg/d orally for 10 days. For children: erythromycin suspension 50 mg/kg per day for 10 to 14 days, clarithromycin suspension 15 mg/kg per day for 10 days, or azithromycin suspension 10 mg/kg on day 1 followed by 5 mg/kg per day once daily on days 2 to 5. Some patients may require retreatment.

Suggested Reading

Black CM, Morse SA. The use of molecular techniques for the diagnosis and epidemiologic study of sexually transmitted infections. *Curr Infect Dis Rep*. 2000;2:31–43

Block S, Hedrick J, Hammerschlag MR, Cassell GH. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in pediatric community-acquired pneumonia. Comparative efficacy and safety of clarithromycin vs. erythromycin ethylsuccinate. *Pediatr Infect Dis J*. 1995;14:471–477

Boman J, Gaydos CA, Quinn TC. Molecular diagnosis of *Chlamydia pneumoniae* infection. *J Clin Microbiol*. 1999;37:3791–3799

Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. *Morbid Mortal Wkly Rep MMWR*. 2002;51(No. RR-6):1–75

Cohen DA, Nsuami M, Martin DH, Farley TA. Repeated school-based screening for sexually transmitted diseases: a feasible strategy for reaching adolescents. *Pediatrics*. 1999;104:1281–1285

Dowell SF, Peeling RW, Boman J, et al. Standardizing *Chlamydia pneumoniae* assays: recommendations from the Centers for Disease Control and Prevention (USA) and the Laboratory Centre for Disease Control (Canada). *Clin Infect Dis*. 2001;33:492–503

Grayston JT, Campbell LA, Kuo CC, et al. A new respiratory pathogen: *Chlamydia pneumoniae* strain TWAR. *J Infect Dis*. 1990;161:618–625

Hammerschlag MR, Ajl S, Laraque D. Inappropriate use of nonculture tests for the detection of *Chlamydia trachomatis* in suspected victims of child sexual abuse: a continuing problem. *Pediatrics*. 1999;104:1137–1139

Hammerschlag MR, Gelling M, Roblin PM, Kutlin A, Jule JE. Treatment of neonatal chlamydial conjunctivitis with azithromycin. *Pediatr Infect Dis J*. 1998;17:1049–1050

Hammerschlag MR, Roblin PM, Gelling M, et al. Use of polymerase chain reaction for the detection of *Chlamydia trachomatis* in ocular and nasopharyngeal specimens from infants with conjunctivitis. *Pediatr Infect Dis J*. 1997;16:293–297

Harris J-A, Kolokathis A, Campbell M, Cassell GH, Hammerschlag MR. Safety and efficacy of azithromycin in the treatment of community acquired pneumonia in children. *Pediatr Infect Dis J*. 1998;17:865–871

Kalayoglu MV, Libby P, Byrne GI. *Chlamydia pneumoniae* as an emerging risk factor in cardiovascular disease. *JAMA*. 2002;288:2724–2731

Kutlin A, Roblin P, Hammerschlag MR. Antibody response to *Chlamydia pneumoniae* infection in children with respiratory illness. *J Infect Dis*. 1998;177:720–724

Rockey DD, Lenart J, Stephens RS. Genome sequencing and our understanding of chlamydiae. *Infect Immun*. 2000;68:5473–5479

PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. Which of the following forms of chlamydiae is responsible for infection?

   A. Elementary body.
   B. Major outer membrane protein.
   C. Nucleus.
   D. Peroxisome.
   E. Reticulate body.

2. A 3-month-old boy presents with difficulty breathing of 2 days' duration. Physical examination documents a rectal temperature of 96.8°F (36°C), respiratory rate of 50 breaths/min, and heart rate of 120 beats/min. Moderate intercostal retractions and grunting are noted. Auscultation reveals bilateral rales. Chest radiography shows diffuse reticular infiltrates throughout the lung fields. Culture from a nasopharyngeal swab yields *Chlamydia pneumoniae*. Of the following, the *most* appropriate antimicrobial agent for this infant is:

   A. Ceftriaxone.
   B. Clindamycin.
   C. Erythromycin.
   D. Tetracycline.
   E. Trimethoprim-sulfamethoxazole.

3. A 2-month-old girl presents with cough, runny nose, and difficulty breathing of 3 days' duration. She was born at term via an uncomplicated vaginal delivery. Physical examination shows an afebrile infant who has a respiratory rate of 54 breaths/min, heart rate of 126 beats/min, intercostal retractions, and audible grunting. On auscultation, rales are heard throughout the lung fields. Chest radiography shows moderate hyperinflation and patchy alveolar infiltrates. Culture from a nasopharyngeal swab is positive for *Chlamydia trachomatis*. Of the following, the *most* likely method by which this infection was acquired is via:

   A. Contaminated fomites.
   B. Droplet infection.
   C. Orofecal route.
   D. Passage through the birth canal.
   E. Transplacental infection.

4. An 18-year-old boy presents with painful urination for the past 4 days. Two months ago, he was treated with a single dose of azithromycin for *C trachomatis* urethritis. He has been sexually active with a single partner. Physical examination reveals moderate whitish urethral discharge. Polymerase chain reaction test of a urethral swab is positive for *C trachomatis*. Of the following, the *most* likely reason for recurrence of his symptoms is:

   A. Coinfection with *C pneumoniae*.
   B. Inadequate treatment.
   C. Microbial resistance to azithromycin.
   D. Reinfection from the untreated partner.
   E. Self-inoculation from a colonized nasopharynx.

Chlamydia trachomatis and Chlamydia pneumoniae Infections in Children and Adolescents

Margaret R. Hammerschlag

Pediatrics in Review 2004;25;43
DOI: 10.1542/pir.25-2-43