Chlamydial Infections in Children and Adolescents

Latha Chandran and Rachel Boykan

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Latha Chandran, MD, MPH,* Rachel Boykan, MD†

Author Disclosure
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Objectives

After completing this article, readers should be able to:

1. Describe the varied clinical manifestations of *Chlamydia trachomatis* infection in neonates, children, and adolescents.
2. Know the clinical manifestations of *Chlamydophila pneumoniae* infection.
3. List the various diagnostic criteria and methods for *C trachomatis* and *C pneumoniae* infections.
4. Discuss the treatments for *C trachomatis* and *C pneumoniae* infections.

Introduction

Chlamydiae are obligate intracellular organisms that cause a wide spectrum of human and animal disease, including conjunctivitis, pneumonia, and genital tract infections. *C trachomatis* and *C pneumoniae* are significant human pathogens; *C psittaci* is a less common cause of human disease.

The earliest descriptions of what is believed to have been trachoma are found in ancient Chinese and Egyptian manuscripts. In 1907, Halberstaedter and von Prowazek found what they assumed (correctly) to be the causal agent in trachoma when they noted intracytoplasmic vacuoles with numerous particles in Giemsa-stained epithelial cells. Subsequently, similar inclusions were described in specimens taken from the eyes of babies who had ophthalmia neonatorum, from their mothers' uteruses, and from men who had urethritis. From 1929 to 1930, outbreaks of an "atypical pneumonia" acquired from psittacine birds stimulated more research, which led to Bedson's description of the characteristic developmental life cycle of all *Chlamydiales*. His accurate description of "an obligate intracellular parasite with bacterial affinities" was not fully appreciated for several decades because these new agents initially were believed to be viruses.

Classification

Under the 2000 taxonomy, the order *Chlamydiales* was divided into four families: *Chlamydiaceae, Parachlamydiaceae, Waddliaceae*, and *Simkaniaceae*. The family *Chlamydiaceae* was divided further into two genera, *Chlamydophila* and *Chlamydia*, based on ribosomal sequence analysis that showed less than 95% homology between *Chlamydia* and *Chlamydophila*. *Chlamydophila* includes the species *C pneumonia, C psittaci*, and nonhuman pathogens; the family *Chlamydia* includes *C trachomatis* and nonhuman pathogens. (1)

Structure and Developmental Cycle

Chlamydiae are obligate intracellular bacteria that have a unique biphasic developmental cycle alternating between an infectious "elementary body" (EB) form and a metabolically active "reticulocyte body" (RB) form (Figure). The EB is believed to be endocytosed into the host cell via a membrane-bound vacuole called an "inclusion." This vacuole avoids phagolysosomal fusion and, hence, detection by the human immune system. Within 8 to 18 hours after

Abbreviations

CDC:	Centers for Disease Control and Prevention
EB:	elementary body
FDA:	Food and Drug Administration
Ig:	immunoglobulin
LGV:	lymphogranuloma venereum
MIF:	microimmunofluorescence
MOMP:	major outer membrane protein
NAAT:	nucleic acid amplification test
RB:	reticulocyte body
WHO:	World Health Organization

*Editorial Board.
†Assistant Professor of Pediatrics, Stony Brook University Medical Center, Stony Brook, NY.

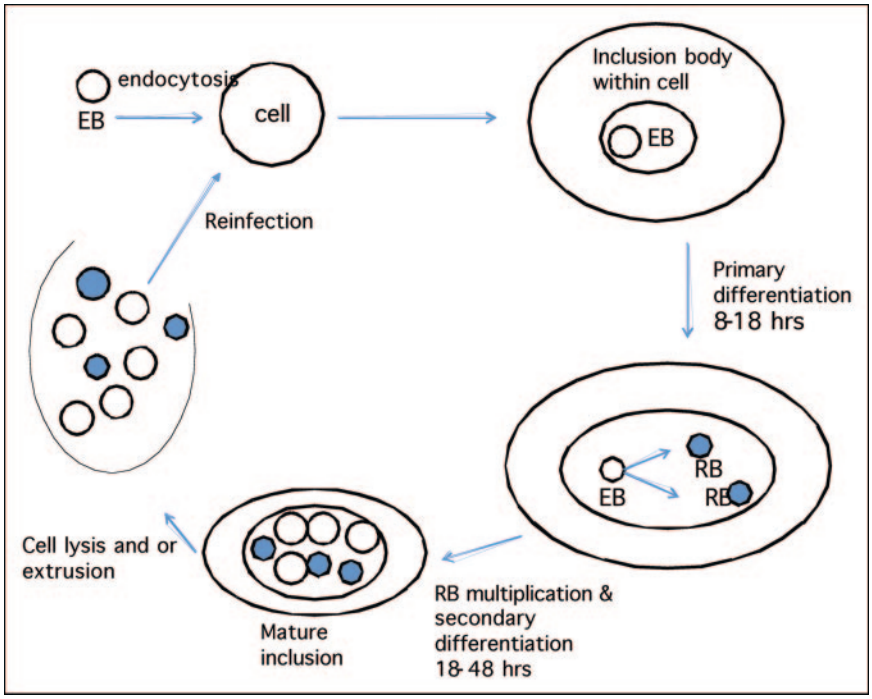

Figure. The life cycle of *Chlamydia trachomatis*. The infectious "elementary body" (EB) is endocytosed into the host cell via a membrane-bound vacuole called an "inclusion body." The EB then undergoes primary differentiation to form reticulocyte bodies (RBs), which subsequently replicate and undergo secondary differentiation back to EBs. Cell lysis or extrusion results in release of EBs, which infect new host cells.

endocytosis, the EB undergoes primary differentiation to form RBs. Between 18 and 36 hours after endocytosis, RBs replicate by repeated cycles of binary fission. Between 36 and 72 hours after endocytosis, the RB undergoes secondary differentiation back to the EB, with subsequent cell lysis and release of new EBs to infect other cells. The indolent and subacute nature of chlamydial infection might be explained by its occult presence within the vacuoles and its long cell cycle.

Common to both the EB and the RB forms of the organism is the major outer membrane protein (MOMP), considered to be integral to the infective nature of *Chlamydia*. This antigen and its antibody have been used extensively in the development of diagnostic tests for *C trachomatis*.

Chlamydia trachomatis Infection

C trachomatis is responsible for a wide range of clinical diseases, including neonatal conjunctivitis, trachoma, pneumonia in young infants, genital tract infection, and lymphogranuloma venereum (LGV). In addition, evidence suggests that chlamydial infection in pregnancy contributes to preterm birth.

C trachomatis has at least 18 serologic variants, of which serovars A through K are responsible for ocular infections and serovars L1, L2, and L3 for LGV. Trachoma usually is caused by serovars A through C, and genital and perinatal infections are caused by serovars B and D through K.

Neonatal Conjunctivitis

C trachomatis is the most frequently identified infectious cause of neonatal conjunctivitis; it is transmitted perinatally by infected mothers. The prevalence of *Chlamydia* infection among pregnant women may be as high as 18%, especially among pregnant adolescents. Infected mothers transmit *Chlamydia* to babies born vaginally 50% of the time; those born by caesarean section who have intact membranes also may be infected. Approximately 25% to 50% of perinatally infected infants develop conjunctivitis. Symptoms include conjunctival edema, hyperemia, and watery-to-mucopurulent discharge. The symptoms typically develop 5 to 14 days after birth and can last for longer than 2 weeks. A pseudomembrane may form and bloody discharge may be present if infection is prolonged. Routine topical prophylaxis with silver nitrate, erythromycin, or tetracycline given to all infants to prevent neonatal gonococcal conjunctivitis is ineffective against chlamydial conjunctivitis. When chlamydial conjunctivitis is diagnosed in an infant, the infant's mother and her sexual partner(s) must be tested. If treated, symptoms of chlamydial conjunctivitis resolve; untreated infections may result in corneal and conjunctival scarring.

Neonatal Pneumonia

Pneumonia due to *C trachomatis* generally presents as a subacute infection 2 to 19 weeks after birth. The incidence of neonatal pneumonia among infants born to infected women is believed to be between 5% and 30%. Patients generally are afebrile. Presenting signs and symptoms include tachypnea, staccato cough, crackles (rales), and rarely, wheezing. Preterm infants may have episodes of apnea. Such signs and symptoms may be preceded by rhinorrhea, congestion, or conjunctivitis.

Chest radiography reveals infiltrates and hyperinflation, but lobar consolidation and pleural effusions usually are not present. Laboratory testing may reveal peripheral eosinophilia and elevated serum immunoglobulins. A positive nasopharyngeal culture is considered diagnostic of infection. However, antibiotic treatment should be started presumptively on clinical grounds. If untreated, symptoms can last for months and include persistent hypoxemia. Diagnosis of chlamydial pneumonia in an infant necessitates treatment of the infant's mother and her sexual partner(s).

Genital Tract Infection

Lower genital tract infection with *C trachomatis* in prepubescent females generally is asymptomatic, although vaginitis sometimes occurs. Perinatally acquired vaginal and rectal infection may persist asymptomatically for up to 18 months after birth, beyond which the possibility of sexual abuse must be considered. (2) In postpubertal girls, chlamydial infection is sexually transmitted and presents as urethritis, cervicitis, endometritis, salpingitis, or perihepatitis. Most cases of urethritis in this age group are due to chlamydial infection; vaginitis is not a common manifestation. Approximately 40% of women whose chlamydial infection is untreated develop pelvic inflammatory disease; 20% of these women may become infertile.

Chlamydial infection is the sexually transmitted infection reported most commonly in the United States, with an increasing estimated prevalence of more than 2,800,000 women. The highest rates occur among adolescent females 14 to 24 years of age. (3) As newer, noninvasive testing (Table 1) has become more available, considerable interest has been expressed in establishing acceptable screening strategies in this population. Because most infected individuals are asymptomatic, the prevalence likely is underestimated. Approximately 5% to 15% of routinely screened women younger than 25 years of age are infected with *C trachomatis*. Recurrence rates of up to 30% have been reported within a few months of initial diagnosis.

Because of the increasing risk of chlamydial infection in young women, both the Centers for Disease Control and Prevention (CDC) and the United States Preventive Services Task Force recommend annual *Chlamydia* screening for all sexually active women younger than age 25 years and for all pregnant women in the first trimester of pregnancy. (3)(4) In addition, the CDC recommends that heterosexual partners of infected women be treated and that all women be retested for *Chlamydia* approximately 3 months after treatment.

Trachoma

Trachoma, the most common infectious cause of blindness worldwide, is a chronic follicular keratoconjunctivitis with corneal neovascularization resulting from untreated or chronic infection. Blindness occurs in up to 15% of those infected. The World Health Organization (WHO) estimates that 6 million people in the world are blind as a result of trachoma and that more than 150 million individuals are infected. Trachoma is highly prevalent in socioeconomically disadvantaged areas where there is crowding and an inadequate clean water supply for basic hygiene. Depending on socioeconomic conditions, the world-wide prevalence of trachoma ranges from 3% to 40% of the population. Trachoma rarely occurs in the United States.

Active infection occurs primarily in young children (<10 years) and generally causes a mild, self-limited conjunctivitis that frequently is asymptomatic. Chronic, or cicatricial, disease, with subsequent scarring and blindness, occurs primarily in adults. Transmission is by direct contact with secretions from the eyes, nose, or throat or by fomites. The diagnosis is made on clinical grounds. Because of the largely asymptomatic nature and high prevalence of this disease, the WHO recommends periodic community-wide distribution of antibiotics such as azithromycin or topical tetracycline in certain areas of high prevalence. The WHO and the Alliance for the Global Elimination of Blinding Trachoma are involved in a campaign to eradicate trachoma by the year 2020 by combining interventions such as **s**urgery, **a**ntibiotics, **f**acial cleanliness, and **e**nvironmental improvement (SAFE). (5)

Diagnostic Testing (Table 1)

Culture is the gold standard for diagnosing *C trachomatis* and is approved by the United States Food and Drug Administration (FDA) for use at all collection sites. Standard collection sites include the endocervix, male and female urethra, nasopharynx, conjunctiva, vagina, and rectum. In all medicolegal cases, culture is the preferred method for confirming the diagnosis. Because *Chlamydia* sp are obligate intracellular organisms, specimens must contain epithelial cells. They should be obtained by using an aluminum-shafted Dacron®-tipped swab and transported and processed under specific temperature guidelines. Wooden or calcium alginate swabs should not be used because they may inhibit growth of the organism. After 48 to 72 hours of incubation, infected cells develop characteristic intracytoplasmic inclusions that subsequently are stained with fluorescent-

Table 1. **Methods of Testing for *Chlamydiae* Species**

Test Name	Test Details	Pros	Cons	Comments
Culture	Requires incubation for 48 to 72 hours	• Gold standard • Highly specific (98% to 100%) and sensitive	• Labor-intensive and expensive • Less sensitive compared with NAAT	Approved for use with specimens from all collection sites Must use aluminum-shafted Dacron®-tipped swab and obtain epithelial cells Preferred method for medicolegal cases
Nucleic acid amplification tests (NAAT): polymerase chain reaction (PCR), transcription-mediated amplification (TMA), strand-displacement amplification (SDA)	Amplification of nucleic acid sequences specific for the organism of interest. May be able to detect organism from as little as a single copy of DNA or RNA	• Highly sensitive and specific (>95%), rapid turnaround time	• Potential for cross-contamination of specimens may lead to false-positive results • Specimens may contain amplification inhibitors, leading to false-negative results	The ease of using urine specimens and the high sensitivity and specificity make it especially useful for large-scale screening, increasing the likelihood that the most at-risk population (adolescent females) will be tested and treated
Nucleic acid probe (NAP)	DNA or RNA probe hybridizes with a specific sequence (RNA or DNA)	• Less expensive than NAAT or culture	• Sensitivity approximately 60% to 70%	Not approved for rectal, vaginal, or respiratory specimens
Enzyme immunoassay (EIA)	Antigen detection test, detects chlamydial LPS with a monoclonal or polyclonal antibody labeled with an enzyme	• Useful for large-scale screening, especially where prevalence is low • Rapid turnaround time	• Sensitivity and specificity approximately 60% to 70%	Cannot be used on rectal specimens because of potential for cross-reaction with fecal bacteria
Direct fluorescent antibody (DFA)	Antigen detection test, detects either LPS or MOMP	• Relatively inexpensive • If anti-MOMP-positive, may be very specific	• If LPS is used, may cross-react with other species • Lower sensitivity (50%), so not used for general screening • Requires technical expertise	
Point of care tests: rapid test DFA, optical immunoassay	Similar to EIAs Use antibodies against LPS	• Fast (<30 min) • Useful if results needed immediately	• Many false-positive results	

LPS=lipopolysaccharide, MOMP=major outer membrane protein

labeled monoclonal antibody specific for the MOMP of *C trachomatis*.

Nucleic acid amplification tests (NAATs) amplify nucleic acid sequences specific for the organism of interest. Various commercial tests use different target nucleic acid sequences and amplification methods. Examples of NAATs include polymerase chain reaction, transcription-mediated amplification, and strand-displacement amplification. NAATs do not require viable organisms and can detect the target of interest from as little as a single copy of DNA or RNA. For this reason, their sensitivity approaches 98%, which is significantly greater than that of

Table 2. Sites of *Chlamydia trachomatis* Infection and Testing Options

Site of Infection	Preferred Test	Other Tests*
Eye	Culture	EIA, NAP, DFA
Nasopharyngeal (for pneumonia)	Culture	DFA, NAAT
Endocervical	NAAT	NAP, EIA, DFA Culture in cases of sexual abuse
Urethral	Culture (women) NAAT (men)	
Urine	NAAT	
Rectum	Culture	DFA

*For several of these tests, Unites States Food and Drug Administration approval is not universal, but manufacturer-specific.
DFA=direct fluorescent antibody test, EIA=enzyme-linked immunosorbent assay, NAAT=nucleic acid amplification test, NAP=nucleic acid probe

culture. Specificity may be close to that of culture. The FDA has approved NAATs for use with endocervical and urethral swabs as well as urine specimens. The ease of using urine specimens, together with the high sensitivity of NAATs, has made these tests the preferred method for screening. NAATs are technically demanding, however, and results vary, depending on the method or laboratory used.

There is no well-established sensitive and specific serum antibody test for *C trachomatis* infection. Many nonculture tests available for the detection of *Chlamydia* have the advantage of being less expensive than culture or NAATs. A summary of the preferred and other options for testing based on the sites of clinical infection is listed in Table 2.

Treatment (Table 3)

Treatment of conjunctivitis and of genital tract infection should be decided on the basis of a positive diagnostic test. Treatment of neonatal pneumonia often is started presumptively based on the clinical picture and radiographic findings suggestive of the diagnosis. Neonatal conjunctivitis due to *C trachomatis* is treated with oral erythromycin. Topical therapies are ineffective. Approximately 10% to 20% of infants treated for conjunctivitis require retreatment. Pneumonia due to *C trachomatis* may be treated with erythromycin or azithromycin. Of note, an association has been described between the use of erythromycin, especially in the first 2 weeks after birth, and an increased risk of pyloric stenosis. *C trachomatis* genital tract infection in adolescents and adults is treated with oral doxycycline or azithromycin. For children younger than 6 months of age, erythromycin is recommended.

Chlamydophila pneumoniae Infection

C pneumoniae causes an atypical pneumonia, with insidious or sudden onset of symptoms of mild-to-severe disease. Manifestations include cough, which may be prolonged from 2 to 6 weeks, and less frequently, sore throat and laryngitis. Extrapulmonary manifestations include nonexudative pharyngitis, bronchitis, acute otitis media, and sinusitis. Clinically, pneumonia due to *C pneumoniae* may be difficult to distinguish from other atypical (eg, *Mycoplasma*) or viral pneumonias. Transmission is presumed to be person-to-person by respiratory droplet, with an incubation period of approximately 21 days. No animal reservoirs are known. Chest radiography may show one or more areas of patchy infiltration; the white blood cell count generally is normal.

Pneumonia due to *C pneumoniae* is seen worldwide. In the United States, it is seen most commonly in children ages 5 to 15 years of age; in developing nations, it has a younger peak age of presentation. Diagnosis is made on clinical grounds, although there are no definitive diagnostic criteria. Patchy infiltrates on chest radiography may suggest the diagnosis. *C pneumoniae* is considered responsible for 6% to 22% of lower respiratory infections in children. In general, infection with *C pneumonia* is short-lived and does not confer persistent immunity.

Serologic testing, specifically microimmunofluorescence (MIF), is the only approved method of diagnosis and, therefore, is the reference standard for other diagnostic methods. Acute *C pneumoniae* infection is defined as a single immunoglobulin M (IgM) titer of at least 1:16 or a greater than fourfold increase in IgG titer by MIF. In primary infections, IgM antibodies do not appear until 2 to 3 weeks; IgG antibodies appear in 6 to 8 weeks. Therefore, MIF is not useful for making a prospective diagnosis. Despite being the "gold standard," MIF is an insensitive test, especially in children, compared with culture. Polymerase chain reaction, enzyme-linked immunosorbent assay, and direct fluorescent antibody testing are other available tools for diagnosis that have varying advantages and disadvantages, as with their use for detecting *C trachomatis*.

Treatment

Treatments include erythromycin (40 to 50 mg/kg per day divided QID), azithromycin (10 mg/kg per day on

Table 3. **Treatments for *Chlamydia trachomatis* Infection**

Infection	Preferred Treatment	Other Options	Comments
Neonatal conjunctivitis	Erythromycin PO 50 mg/kg per day in four divided doses×14 days	Older than 1 month of age: sulfisoxazole PO, 150 mg/kg per day divided q 4 to 6 hours	Topical therapy ineffective Re-treat with repeat course of erythromycin if necessary
Neonatal pneumonia	Erythromycin PO 50 mg/kg per day in four divided doses×14 days	Azithromycin, 20 mg/kg per day, once daily×3 days, sulfonamide PO	
Genital tract infection (adolescents and adults)	Doxycycline PO 200 mg/day in two divided doses×7 days or azithromycin, 1 g single oral dose	Erythromycin base PO 2 g/day in four divided doses for 7 days (maximum dose, 2 g/day) Levofloxacin 500 mg PO once daily for 7 days	
Genital tract infection (children)	6 months–12 years: Erythromycin PO 50 mg/kg per day in three to four divided doses for 7 days (maximum, 2 g/day), azithromycin PO 10 mg/kg followed by 5 mg/kg, not to exceed 250 mg/d on days 2 to 5 <6 months old: Erythromycin PO at above dose		
Trachoma	Topical therapy with erythromycin, tetracycline, sulfacetamide ointment, various schedules	Erythromycin or doxycycline PO (>8 years of age), azithromycin	Difficult to treat and to track treatment success
Lymphogranuloma venereum	>9 years old: Doxycycline PO, 200 mg/day in three divided doses×21 days	Erythromycin×21 days (recommended by some, but data lacking)	

day 1 followed by 5 mg/kg per day for 4 more days), or clarithromycin (15 mg/kg per day divided BID) or doxycycline (4 mg/kg per day divided BID) for those older than 8 years of age.

Chlamydophila psittaci Infection

C psittaci, the cause of psittacosis, may be transmitted by many birds such as parakeets, parrots, macaws, pigeons, and turkeys, which serve as its reservoir. People living or working closely in the environment of sick birds are especially at risk for acquiring the disease. Psittacosis occurs worldwide and may occur sporadically. This infection is relatively rare in children. The incubation period is 5 to 14 days or longer. In contrast to infection with *C pneumoniae*, psittacosis is characterized by the abrupt onset of fever, nonproductive cough, headache, and malaise. The radiographic finding of interstitial infiltrates may be worse than the clinical picture. Rare extrapulmonary complications include pericarditis, myocarditis, endocarditis, hepatitis, and encephalopathy. *C psittaci* infection is diagnosed by a fourfold increase in acute and convalescent serum antibody concentrations. The treatment of *C psittaci* infections is similar to that of *C pneumoniae* infections.

Areas for Additional Research

C pneumoniae has been proposed as a causative agent in asthma and atherosclerosis. This proposal makes intuitive sense because *C pneumoniae* is an intracellular organism that tends to lead to prolonged, often repeated infections. However, studies to date have yielded conflicting data about its protective role in asthma versus its causative role in the disease. The proposed association between this organism and atherosclerosis currently is being investigated prospectively.

Summary

Chlamydial infections are highly prevalent and affect all age groups. Most are indolent and subacute, potentially resulting in long-term morbidity, including chronic pelvic pain, infertility, and trachoma-related blindness. Several available diagnostic tests have varying degrees of sensitivity, specificity, and clinical utility. The NAAT tests have greatly improved the ability to conduct

population-based screening for *Chlamydia*. Preferred diagnostic methods vary, based on the site of infection. Chlamydial infections are easily treated with macrolide antibiotics. The role of *Chlamydia* in the pathogenesis of asthma and atherosclerosis is under investigation.

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PIR Quiz

Quiz also available online at pedsinreview.aappublications.org.

1. A previously healthy 10-day-old girl is brought to your office with a 2-day history of bilateral watery eye discharge with hyperemia. She has been afebrile and is breastfeeding normally. The pregnancy was complicated by *Chlamydia* infection in the first trimester, for which the mother was treated. After establishing that the infant has *Chlamydia* conjunctivitis, the *most* appropriate treatment is:

   A. Azithromycin 1 g single oral dose.
   B. Azithromycin ophthalmic 1% solution 1 drop in each eye QD×7 days.
   C. Erythromycin 50 mg/kg per day in 4 divided oral doses×14 days.
   D. Erythromycin ophthalmic ointment applied to the eyelids BID×10 days.
   E. Sulfisoxazole 150 mg/kg per day in six divided oral doses×14 days.

2. You are discussing the increasing prevalence of *Chlamydia* with a group of medical students. You explain that the *most* sensitive screening method for detecting infection in adolescent girls is:

   A. Direct fluorescent antibody testing.
   B. Enzyme immunoassay on urine specimens.
   C. Nucleic acid amplification test performed on urine specimens.
   D. Nucleic acid probe performed with either urine or cervical specimens.
   E. Urine or cervical specimen culture.

3. You suspect that a 3-year-old girl has been sexually abused. Among the following, the method of testing for *Chlamydia* that is considered the solid standard and, thus, preferred in a court of law is:

   A. Culture.
   B. Direct fluorescent antibody.
   C. Enzyme immunoassay.
   D. Nucleic acid amplification.
   E. Nucleic acid probe.

4. A 4-year-old girl has a history of intermittent vaginal erythema and clear discharge. She is afebrile, and there are no other positive findings on physical examination. Culture of vaginal fluid from the posterior fornix is positive for *Chlamydia*. Of the following, the *most* appropriate next step is:

   A. Confirmation of the diagnosis by using a direct fluorescent antibody technique.
   B. Confirmation of the diagnosis by using a nucleic acid amplification test.
   C. Notification of Child Protective Services for suspected sexual abuse.
   D. Treatment with ceftriaxone 50 mg/kg per day×7 days.
   E. Treatment with doxycycline 200 mg/d×7 days.

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