Chlamydia trachomatis in Children

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The genus Chlamydia is a group of obligate intracellular parasites with a unique developmental cycle of morphologically distinct reproductive and infectious forms. All members of the genus have a gram-negative envelope without peptidoglycan, share a genus-specific lipopolysaccharide antigen, and use host adenosine triphosphate for the synthesis of chlamydial protein. The genus now contains three species, Chlamydia trachomatis, Chlamydia psittaci, and the recently described Chlamydia pneumoniae (TWAR). There are 15 known serotypes of C trachomatis.

The chlamydial developmental cycle involves an infectious, metabolically inactive extracellular form (elementary body) and a noninfectious, metabolically active intracellular form (reticulate body). Elementary bodies, which are 200 μm to 400 μm in diameter, attach to the host cell by a process of electrostatic binding and are taken into the cell by endocytosis that is not dependent on the microtubule system. Within the host cell, the elementary body remains within a membrane-lined phagosome. Fusion of the phagosome with the host cell lysosome does not occur. The elementary bodies then differentiate into reticulate bodies that undergo binary fission. After approximately 36 hours, the reticulate bodies differentiate into elementary bodies. At about 48 hours, release may occur by cytolyosis or by a process of exocytosis or extrusion of the whole inclusion, leaving the host cell intact.

Approximately 50% to 75% of infants born to chlamydial-infected women will become infected at one or more anatomic sites, including the conjunctiva, nasopharynx, rectum, and vagina.

EPIDEMIOLOGY

Chlamydia trachomatis is probably the most prevalent sexually transmitted infection in the United States today. The Centers for Disease Control and Prevention (CDC) estimate that the number of new C trachomatis infections exceeds 4 million annually.
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The prevalence of chlamydial infection is more weakly associated with socioeconomic status, urban/rural residence, and race/ethnicity than are gonorrhea and syphilis. Prevalence of *C. trachomatis* infections 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 the race or ethnicity of the population. Among sexually active adolescents, prevalence commonly exceeds 10% and may exceed 20%. Decreasing age at first intercourse and increasing age at marriage have contributed importantly to the higher prevalence of *C. trachomatis* infection. 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. Children also may acquire chlamydial infection as a result of sexual abuse.

INFECTIONS IN INFANTS

Pregnant women who have cervical infection with *C. trachomatis* can transmit the infection to their infants who subsequently may develop neonatal conjunctivitis and pneumonia. Epidemiologic evidence strongly suggests that the infant acquires the chlamydial infection from the mother during vaginal delivery. Infection after caesarean section is rare and usually occurs after early rupture of the amniotic membrane. There is no evidence supporting nonsexual postnatal acquisition from the mother or other family members. Approximately 50% to 75% of infants born to chlamydial-infected women will become infected at one or more anatomic sites, including the conjunctiva, nasopharynx, rectum, and vagina (Table 1).

INCLUSION CONJUNCTIVITIS

*Chlamydia trachomatis* is the most frequent identifiable infectious cause of neonatal conjunctivitis and the major clinical manifestation of neonatal chlamydial infection. Approximately 30% to 50% of infants born to chlamydial positive mothers will develop conjunctivitis. Studies from our and other institutions have identified *C. trachomatis* in 30% to 40% of infants younger than 1 month of age presenting with conjunctivitis. The incubation period is 5 to 14 days after delivery, or earlier if there has been premature rupture of membranes. Infection is rare following caesarean section with intact membranes but can happen. At least 50% of infants with chlamydial conjunctivitis also will have nasopharyngeal infection. The presentation is extremely variable, ranging from mild conjunctival injection with scant mucoid discharge to severe conjunctivitis with copious purulent discharge, chemosis, and pseudomembrane formation. The conjunctiva can be very friable and may bleed when stroked with a swab. Chlamydial conjunctivitis needs to 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. There can be overlap in both incubation periods and presentation.

PNEUMONIA

The nasopharynx is the most frequent site of perinatally acquired chlamydial infection. Approximately 70% of infected infants will have positive cultures at that site. The majority of these nasopharyngeal infections are asymptomatic and colonization may persist for 3 years or more. Chlamydial pneumonia develops in about 30% of infants with nasopharyngeal infection. In those infants who develop pneumonia, the presentation and clinical findings are characteristic. The infants 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. Frequently, the infants have a history of a persistent staccato cough and congestion with an absence of fever. On physical examination, the infant is tachypneic and rales are heard on auscultation of the chest. Wheezing is uncommon. There are no specific radiographic findings except hyperinflation. Significant laboratory findings include peripheral eosinophilia (>300 cells/mL) and elevated serum immunoglobulins.

INFECTIONS AT OTHER SITES

Infants born to chlamydia-positive mothers also may become infected in the rectum and vagina. Although infection at these sites appears to be totally asymptomatic, the infection may cause confusion if detected at a later date. Schachter et al reported finding subclinical rectal and vaginal infection in 14% of infants born to chlamydia-positive women; some of these infants were still culture positive at 18 months of age. Bell et al were able to follow 22 infants born to women with culture-proven chlamydial infections and found that positive cultures were detected in the nasopharynx or oropharynx of some of these children as late as 28½ months after birth. Nine infants had rectal or vaginal infections.
TABLE 1

Selected Studies of Perinatal Chlamydial Infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence of Maternal Genital Infection</th>
<th>Proportion of Infants Born to Infected Mothers Who Developed Chlamydial Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No.</td>
<td>Infected (%)</td>
</tr>
<tr>
<td>Frommell, 1979, San Francisco</td>
<td>340</td>
<td>30 (8.8)</td>
</tr>
<tr>
<td>Hammerschlag, 1980, Seattle</td>
<td>317</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Schachter, 1986, San Francisco</td>
<td>5531</td>
<td>262 (4.7)</td>
</tr>
</tbody>
</table>

Abbreviations: NP = nasopharyngeal and NS = not studied.

that persisted for slightly over 12 months. There are anecdotal reports of perinatally acquired rectal, vaginal, and nasopharyngeal infections persisting for at least 3 years. This needs to be kept in mind when evaluating children for suspected sexual abuse.

INFECTIONS IN OLDER CHILDREN

Chlamydia trachomatis has not been associated with any specific clinical syndrome in older infants and children. Most attention to C. trachomatis infection in these children has concentrated on the relationship to child sexual abuse. It has been suggested that the isolation of C. trachomatis from a rectal or genital site in children without 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 periods up to 3 years. This is an important confounding variable.

Vaginal infection with C. trachomatis was reported uncommonly in prepubertal children before 1980. The possibility of sexual contact usually was not discussed. In 1981, Rettig et al. reported concurrent or subsequent chlamydial infection in 9 of 33 (27%) episodes of gonorrhea in a group of prepubertal children. This compares with rates of concurrent infection in men and women of 1% to 62%, depending on the study. However, C. trachomatis was not found in any of 31 children presenting with urethritis or vaginitis that was not gonococcal. No information was given about possible sexual activity.

Recent studies have identified rectal and genital chlamydial infection in 2% to 13% of sexually abused children when these children were routinely cultured for the organism (Table 2). The majority of those with chlamydial infection were asymptomatic. In two early studies that had control groups, similar percentages of control patients also were infected. The control group in one study consisted of children who had been referred for evaluation of possible sexual abuse but were found to have no history of sexual contact and siblings of abused children. The mean age of this group was 4½ years compared with 7½ years for the group with a history of sexual contact, thus suggesting a bias related to the inability to elicit a history of sexual contact from young children. In the second study, the control group was selected from a well-child clinic. Three girls in this group were found to have positive chlamydial cultures. Two who had positive vaginal cultures were sisters who had been sexually abused 3 years previously and had not received interim treatment with antibiotics. The implication of this observation was that these children were infected for at least 3 years and were asymptomatic. The remaining control child with C. trachomatis isolated from her throat and rectum had no history of sexual contact.

A subsequent larger study by Ingram et al. found a stronger association between vaginal chlamydial infection and a history of sexual abuse, but not with pharyngeal infection, which was found in a similar number of controls (Table 2). Rectal infection was detected in only 1 of 124 abused children.

The possibility of prolonged perinatally acquired vaginal or rectal carriage in the sexually abused group was minimized in the study by Hammerschlag et al. Chlamydial cultures obtained at the initial examination were negative, and the infection was only detected at follow-up examination 2 to 4 weeks later. However, the two abused girls who had developed chlamydial infection were victims of a single assault by a stranger. In the setting of repeated abuse by a family member over long periods of time, development of infection would be difficult to demonstrate. Among adolescents and adults who are victims of sexual assault, acquisition of C. trachomatis is uncommon, less than 2% over the rate found at baseline.
TABLE 2

Prevalence of Chlamydia trachomatis Infections in Sexually Abused Children and Controls

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Cases (%)</th>
<th>No. Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Vagina</td>
<td>Rectum Pharynx</td>
</tr>
<tr>
<td>Ingram et al1</td>
<td>50</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Hammerschlag et al2</td>
<td>50</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Ingram et al3</td>
<td>124</td>
<td>10 (8)</td>
</tr>
</tbody>
</table>

*These two children had a history of sexual abuse by their stepfather 3 years prior to examination.

The 1993 Sexually Transmitted Diseases Treatment Guidelines of the CDC has dropped the recommendation that cultures for C trachomatis be obtained routinely from the pharynx and urethra in children who are suspected victims of sexual abuse.16 The major reasons for this were the low yield from the urethra, the tendency for longer persistence of perinatally acquired pharyngeal infection, and the potential confusion with C pneumoniae.

DIAGNOSIS OF CHLAMYDIA TRACHOMATIS INFECTIONS IN CHILDREN

The diagnostic gold standard remains isolation by culture of C trachomatis 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.1 Several nonculture methods have approval of the Food and Drug Administration (FDA) for diagnosis of chlamydial conjunctivitis. They include enzyme immunoassays (EIAs), specifically Chlamydiazyme (Abbott Diagnostics, North Chicago, Illinois), Pathfinder (Sanofi-Pasteur, Chaska, Minnesota) and SureCell (Kodak, Rochester, New York) and direct fluorescent antibody tests (DFA), including Syva MicroTrak (Genetic Systems, Seattle, Washington) and Pathfinder. These tests appear to perform very well with conjunctival specimens with sensitivities ≥90% and specificities ≥95% compared with culture.4 Unfortunately, the performance with nasopharyngeal specimens has not been as good.

Although one commercially available deoxyribonucleic acid (DNA) probe, Pace II (GenProbe, San Diego, California) has become perhaps the most widely used nonculture test for the diagnosis of chlamydial infections in many parts of the country, it has FDA approval only for cervical and urethral sites in adults, where its performance has been similar to most of the approved EIAs available. It does not have approval for any site in children, including the conjunctiva, vagina, or rectum. The recently approved polymerase chain reaction assay, Amplicor (Roche, Nutley, New Jersey), also has approval only for genital sites in adults and has not been evaluated for any site in children.

It should be emphasized that nonculture tests should never be used for rectal or vaginal sites in children or for any forensic purposes in adolescents and adults. This is stated clearly in the CDC’s 1993 Chlamydia Guidelines1 and 1993 Sexually Transmitted Diseases Treatment Guidelines.16 There are no exceptions. Use of these tests for vaginal and rectal specimens has been associated with a large number of false-positive tests.17-19 Fecal material can give false-positive reactions with any EIA; none are approved for this site in adults. Common bowel organisms, including Escherichia coli, Proteus species, vaginal organisms such as group B streptococcus and Gardnerella vaginalis, and even some respiratory flora such as group A streptococcus also can give positive reactions with EIAs.19 These types of tests are best for screening for genital infection in adolescents and adults in high-prevalence populations (prevalence of infection ≥7%).4 There are few reports on the performance of the DNA probe, but it appears to be equivalent to most available EIAs in terms of sensitivity and specificity compared to culture for genital specimens.

Another potential problem can occur with use of an EIA for respiratory specimens. As all of the available EIAs use genus-specific antibodies, if used for respiratory specimens, these tests also will detect C pneumoniae.

Even though culture is considered the gold standard, culture of C trachomatis is not regulated in any way, and sensitivity may vary from laboratory to laboratory.1 The methods used for culture confirmation became an issue when several large commercial laboratories started using EIA instead of folic acid staining and visual identification of inclusions for culture confirmation. This has resulted in at least one "outbreak" of falsely identified C trachomatis infection among residents and staff of an institution for the mentally retarded in Ohio in 1990.20 All of the "positive" cultures, mostly rectal specimens, were subsequently determined to be false-positives result-
ing from carry-over of fecal material and bacteria in
the culture specimens.

The major advantage of culture is that it is 100% specific. When cultures are obtained for Chlamydia in the evaluation of suspected sexual abuse, one should pay careful attention to the laboratory used. Unlike Canada, we do not have a system of designated reference laboratories.

TREATMENT

Because of its long growth cycle, treatment of chlamydial infections requires multiple dose regimens. None of the currently recommended single-dose regimens for gonorrhea are effective against Chlamydia.

TREATMENT OF CHLAMYDIAL CONJUNCTIVITIS AND PNEUMONIA IN INFANTS

Oral erythromycin suspension (ethylsuccinate or stearate), 50 mg/kg/day for 10 to 14 days is the therapy of choice for chlamydial conjunctivitis in infants. It provides better and faster resolution of the conjunctivitis as well as treating any concurrent nasopharyngeal infection, which will prevent the development of pneumonia. Additional topical therapy is not needed. The efficacy of this regimen has been reported to range from 80% to 90%; thus, 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 and results in clinical improvement as well as elimination of the organism from the respiratory tract.

TREATMENT OF OLDER CHILDREN

Chlamydial infections may be treated with oral erythromycin, 50 mg/kg/day, four times a day orally to a maximum of 2 g a day for 7 to 14 days. Children older than 8 years of age may be treated with tetracycline, 25 to 50 mg/kg/day four times a day, orally for 7 days. The new macrolide antibiotic, azithromycin, has been approved as single-dose treatment for uncomplicated chlamydial urethral and cervical infection in men and nonpregnant women. Studies with azithromycin suspension in children are currently underway. A study of single-dose treatment of neonatal chlamydial conjunctivitis and respiratory infection with azithromycin is being planned.

REFERENCES