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Review Article

Chlamydia trachomatis Infection Challenge in Infants and Children

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Abstract

Introduction: Babies born to mothers with active *Chlamydia* infection can have a 50 - 75% risk of contracting it. This infection can affect the conjunctiva, nasopharynx, rectum and vagina of the baby. The most common clinical manifestation in neonates is inclusion conjunctivitis. Reported occurs in 15 - 37% of babies born to mothers with cervical *Chlamydia*. Meanwhile, the part of the baby's body most often infected by *Chlamydia* is the nasopharynx. About 78% of infants have positive nasopharyngeal cultures. Approximately half of the infants with inclusion conjunctivitis also become infected with the nasopharynx. *C. trachomatis* infection was also found in children with sexual abuse, with a rarer prevalence below 5%. This infection is also often asymptomatic. The detection of infection in the rectum and vagina is usually found longer than infection of the conjunctivae and nasopharynx. Infections of the rectum and vagina are often asymptomatic. However, it can last for about 1 year.

Discussion: Several studies in the United States show that about 5 percent of neonates are infected with *Chlamydia* perinatally, but the prevalence of childhood antibodies before sexual activity is more than 20 percent. The incidence of childhood infections has not been well detected, but studies have found transmission from infected siblings (where the infection was acquired perinatally for more than 1 year) or from parents or other adults through sexual abuse. Infection in children can affect the upper respiratory tract of children, eyes, or middle ear infected with *C. trachomatis* may explain the difference in antibody levels in the neonatal period and adolescence, in which genital *Chlamydia* infection can be acquired by children as a result of sexual abuse. In comparison, an antibody cross-reaction against *Chlamydia pneumoniae* was performed which primarily infects the upper respiratory tract of children accounting for part or all of the seroprevalence of *C. trachomatis*.

Conclusion: Sexual abuse must be considered a cause of Chlamydial infection in infants and children. However, perinatally transmitted *C. trachomatis* infection of the nasopharynx, urogenital tract and rectum might persist for 2 - 3 years.

Keywords: *Chlamydia* Infection; Infant; Children; Manifestation

Introduction

Chlamydia trachomatis is a pathogenic germ in humans and is one of four species with the genus *Chlamydia*. However, the species that infect humans are *C. trachomatis*, *C. pneumonia* and *C. psittaci* [1]. Each of these species contains many strains that have various serological and biological characteristics. The need for a better means of this specification is indispensable, especially for *C. trachomatis*. *C. trachomatis* species itself contains 4 biovariants which are different organisms. The Murine and Swine variants are not known whether they infect humans [1].

Epidemiological evidence strongly suggests that babies get *Chlamydia* infection from their mothers during labor. This is based on a number of prospective control studies of mother-child infection, where infection only occurs in infants born to infected mothers. No one has yet stated horizontal transmission from mother to child, from other family members to babies or from babies to other babies after delivery. Infection is rare during cesarean delivery. Infection that often occurs is in the case of premature rupture of the membranes so that contamination is possible [2].

Babies born to mothers with active *Chlamydia* infection can have a 50 - 75% risk of contracting it. This infection can affect the conjunctiva, nasopharynx, rectum and vagina of the baby. The most common clinical manifestation in neonates is inclusion conjunctivitis. Reported occurs in 15 - 37% of babies born to mothers with cervical *Chlamydia*. Meanwhile, the part of the baby's body most often infected by *Chlamydia* is the nasopharynx. About 78% of infants have positive nasopharyngeal cultures. Approximately half of the infants with inclusion conjunctivitis also become infected with the nasopharynx [3].

C. trachomatis infection was also found in children with sexual abuse, with a rarer prevalence below 5%. This infection is also often asymptomatic. The detection of infection in the rectum and vagina is usually found longer than infection of the conjunctivae and nasopharynx. Infections of the rectum and vagina are often asymptomatic. However, it can last for about 1 year [4].

Discussion

The study also found that about 33% of infants with a positive isolation of nasopharyngeal infection developed pneumonia. The risk of developing pneumonia in babies born to mothers with *Chlamydia* is reported to be 1 - 22%. The risk of infection of the rectum and vagina in infants with *Chlamydia* mothers was reported to be 18.9% and 14.5%. Several studies in the United States show that about 5 percent of neonates are infected with *Chlamydia* perinatally, but the prevalence of childhood antibodies before sexual activity is more than 20 percent. The incidence of childhood infections has not been well detected, but studies have found transmission from infected siblings (where the infection was acquired perinatally for more than 1 year) or from parents or other adults through sexual abuse [5].

Infection in children can affect the upper respiratory tract of children, eyes, or middle ear infected with *C. trachomatis* may explain the difference in antibody levels in the neonatal period and adolescence, in which genital *Chlamydia* infection can be acquired by children as a result of sexual abuse. In comparison, an antibody cross-reaction against *Chlamydia* pneumoniae was performed which primarily infects the upper respiratory tract of children accounting for part or all of the seroprevalence of *C. trachomatis* [6].

Clinical manifestation of *Chlamydia* infection

The main clinical manifestation of *Chlamydia* infection in neonates is neonatal conjunctivitis, of which *C. trachomatis* has been identified as the most frequent cause of the disease. Approximately 30 - 50% of babies born to mothers who have *Chlamydia* infection will develop conjunctivitis. This study has identified *C. trachomatis* in 10 - 40% of infants younger than 1 month old with conjunctivitis. The incubation period is 5 - 14 days after birth or earlier if there is premature rupture of membranes, approximately 50% of babies with conjunctivitis due to *Chlamydia* infection will also have nasopharyngeal infection [1].

The clinical manifestations vary widely, from mild conjunctivitis with dilute mucoid discharge to severe conjunctivitis with thick and purulent discharge, chemosis and pseudomembranous formation. The conjunctiva will be very fragile and bleed easily when swabbed. Edge of the eye erythema and often edema. Gram stain of the conjunctival swab shows predominance of PMN cells. Chlamydial conjunctivitis needs to be differentiated from gonococcal ophthalmic infection in some infants, especially in mothers who did not attend prenatal visits, received gonorrhea infection during pregnancy, and engaged in drug abuse. Neonatal conjunctivitis by *Chlamydia* has been suggested to induce long-term defects because

it can lead to the formation of neovascular corneas and scars [4,7].

The nasopharynx is the site of most *Chlamydia* infection at perinatal age. Nearly 70% of infected infants have positive cultures at this location, whereas nasopharyngeal infection itself is asymptomatic and can last for 3 years or more. *Chlamydia* pneumonia alone occurs in only 30% of infants infected with the nasopharynx. Infection of the nasopharynx is a secondary infection and conjunctivitis or is a direct infection that occurs in the nasopharynx. There are still differences of opinion. During labor, the possible source of infection comes from aspiration of infected cervical secretions. Results from prospective studies of mother-child infections have shown that pneumonia can occur in infants with *Chlamydia* conjunctivitis and it is believed the mechanism is the same. In infants with pneumonia, the clinical manifestations of pneumonia are very typical, including [8,9]:

- In children usually appear at the age of 4 - 8 weeks, some cases were reported to appear earlier, namely at week 2 but no cases appear more than 4 months of age.
- These babies usually have a history of coughing and access without any febrile.
- On physical examination found tachypnea and crackles on auscultation; wheezing is rare.
- On radiological images found only hyperinflammation that is not typical.
- Laboratory tests showed that the number of peripheral blood eosinophils increased (> 300 cells/cm^3) and increased serum immunoglobulin.
- In culture can be found the growth of microorganisms cultured from nasopharyngeal secretions.

Pneumonia in children caused by *C. trachomatis* is self-limited in nature. Most babies can be treated outpatient, but there are also some cases that need to be hospitalized because of obstruction and help with breathing. The diagnosis of *C. trachomatis* can be confirmed by serological examination. A 1:32 increase in IgM antibody titer is a strong sign of *Chlamydia* infection. In addition, *C. trachomatis* can be isolated from the nasopharynx. These infections are associated with decreased pulmonary function and airway obstruction, and infants with *Chlamydia* infection have a higher incidence of chronic respiratory distress than infants with non-*Chlamydia* infections [10].

Laboratory examination

Laboratory tests for *Chlamydia* have progressed rapidly over time. The ideal diagnostic test is one that has a sensitivity greater than 90% and a specificity greater than 99%. The ideal test that should be used is nucleic acid amplification (AAN). However, the use of this test should be adjusted to the capacity of the available health facilities. For screening programs, a technique that uses a non-invasive specimen is usually used [11].

Gram stain

This technique is a faster laboratory test to evaluate urethritis and determine the presence or absence of gonococcal infection. Considered positive for NGU if there are more than 4 leukocytes with 1000 times magnification, but unable to see BE and BR [11].

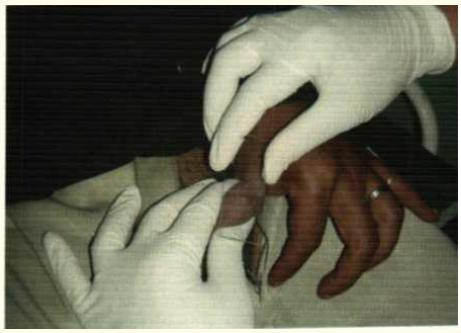

Figure 1: Collection of specimens for gram stain and wet [12].

Urine sediment

Urethritis diagnosis criteria are enforced if there is a urethral body and there are 20 or more PMN leukocytes in two or more of the five fields of view with 400x magnification from the sediment examination of 10 - 15 ml of the first collected urine released before 4 hours or more [12].

Leukocyte esterase test

The approach to screening men with asymptomatic infection for the presence of polymorphonuclear leukocytes uses the urine leukocyte esterase (LE) test. The men were then tested specifically for *Chlamydia* infection or were treated empirically. Most investigators who use culture to determine *Chlamydia* infection, find the sensitivity of the LE test to predict *Chlamydia* urethritis is 41 to 85 percent among asymptomatic men, with a specificity of 75 - 95%.

Some authors conclude that the LE test is less sensitive as a means of screening [12].

Further studies are needed in populations universally screened with DNA amplification assays to clearly define the optimal role of LE in reducing costs. However, in circumstances where there are cost difficulties in implementing tests such as LCR and PCR, the use of an inexpensive LE test is likely to be cost effective, especially when combined with a simple assessment of risk in order to detect a higher probability of developing disease before testing.

Cell culture

Cell culture is the gold standard test for detecting *C. trachomatis* for several years or confirming the presence of this species. Sensitivity 40 - 85% in genital specimens (cervix, urethra). The advantage is high specificity, both for medicolegal diagnosis purposes. The disadvantages of using cell culture [13]:

There are special requirements both in culture and in specimen transport techniques so that cell cultures can be cultured properly;

This technique is suitable for small amounts of invasive samples and requires specimen transport so it is impractical, difficult to perform and requires high costs.

Antigen detection test

The antigen detection test uses *Chlamydia* lipopolysaccharide (LPS) or major outer membrane protein (MOMP), as a means of detecting *Chlamydia* elementary bodies in genital specimens. The most widely used antigen detection tests are the direct fluorescent antibody assay (DFA) and enzyme immunoassays (EIA) assays [14].

Direct fluorescent immunoassay (DFA)

DFA has a sensitivity of 50 - 90% depending on skill and the number of elementary bodies in the specimen. The advantage of this technique is that it is suitable for both invasive and non-invasive specimens (e.g. urine). While the disadvantage is that this test is not suitable for large numbers of specimens and takes time [15].

Enzyme immunoassays (EIA)

This technique has a sensitivity of 20 - 85% depending on the type of test. The advantage is that it can be used to examine large numbers of specimens, is fast and inexpensive. While the disadvantage is that it has a high sensitivity, only if a positive result is confirmed by other tests, it is only suitable for invasive specimens (cervix, urethra) [12].

Nucleic acid hybridization

This test has a sensitivity of 70 - 85%, while the advantage is that it is fast and can be used automatically. Can be used for large samples. Tests can be performed to check the diagnosis of gonococcal infection at the same time. The disadvantage is that it can only be used for invasive specimens (cervix, urethra) [12,15].

Nucleic acid amplification (AAN)

The AAN technique itself has a sensitivity of 70 - 95%. This test has the advantage of high specificity (97 - 99%), which can be used to examine large numbers of specimens. Its use can be on invasive specimens (cervix, urethra) or noninvasive (urine and vulvovaginal), it can be examined to diagnose gonococcal infection simultaneously. The disadvantage of this test is that it is expensive, it needs caution in use to avoid contamination in the laboratory. *Chlamydia* inhibitors, especially in urine specimens, can make this test difficult [13].

Currently there is an automated method for detecting DNA or RNA amplified *C. trachomatis*. The two most widely used methods are ligase chain reaction (LCR) and polymerase chain reaction (PCR). The other method is transcription-mediated amplification (TMA), propagates Chlamydial ribosomal RNA, and appears to have a similar action to LCR and PCR. The target of LCR and PCR is the nucleotide portion of the *C. trachomatis* plasmid, which is present in multiple copies of each elementary body. The TMA target is the ribosomal RNA portion. The lowest limit that can be detected by this test is 1 to 10 elementary bodies (compared to 10,000 elementary bodies for EIA) [14].

In order to determine the function of the new amplification tests, a standard other than cell culture is used, this requires re-evaluation of specimens that are negative on culture and positive on amplification tests. The first confirmation used DFA on cytospin from culture transport media. If the results are negative with DFA, repeat the PCR or LCR again using the test against another target nucleotide part, called the chromosome MOMP gene sequence [15].

There is an alternative approach using 3 available amplification methods to confirm one amplification method using another similar method. Using the developed standard, the application of LCR to

the urine of the first portion (10 - 14 ml from the first stream) has a sensitivity of about 69 to 96% in detecting Chlamydial urethritis in women. The sensitivity of the LCR shown in endocervical specimens ranged from 81 - 100 [12,13].

Compared with cell culture results, LCR generally detects between 15 - 40% infected patients, with an increase in prevalence of 4 - 5%. One study indicated that the LCR shows that endocervical specimens are constantly more sensitive than culture, and that the LCR displays sufficient sensitivity to first-collected urine, meaning it is a noninvasive test that can be used to diagnose *Chlamydia*'s urethral and cervical infection in women. Regarding the effect of inhibitors on endocervical specimens and urine on LCR and PCR, further research is needed [14].

Chlamydia is not significant for diagnosing acute urogenital infections. This is due to the high prevalence rate and the rare increase or decrease in IgG at the onset of infection, and patients are often in periods of absence of IgM. So that the serology test does not have much meaning. Usually, this serological test is widely used for the diagnosis of LGV and pneumonia in neonates [12].

Diagnosis and management of *C. trachomatis* infection in children

The diagnosis of *Chlamydia* ophthalmia was made based on Giemsa's stain of conjunctival scrap and found to be basophilic with intracytoplasmic inclusions. The correlation between cytology and *Chlamydia* culture in *Chlamydia* ophthalmia ranges from 39% to 90%. This method has been replaced by culture and antigen detection tests, such as DFA, EIA and NAA. This test has a sensitivity of > 90% and a specificity of > 95% in conjunctival specimens compared with culture [16].

However, for nasopharyngeal specimens it is not very good. Although the sensitivity to detect *C. trachomatis* in nasopharyngeal specimens of infants with pneumonia is > 90%, the sensitivity in conjunctivitis infants ranges from 38 to 91.7%, DNA Probe, Pace II (Gen Probe) is more commercial, but noncultural tests for diagnosis *Chlamydia* infection has been used widely in several countries [17].

The goal of treatment is to prevent transmission to sexual partners. Therapy on sexual partners is also carried out to prevent reinfection. Therapy for children and infant is still carried out by preventing transmission to sexual harassment. Therapy Indications [18]:

- Established oculogenital *C. trachomatis* infection.
- *C. trachomatis* infection in sexual partners.
- If laboratory tests for *C. trachomatis* are not available, the patient has been confirmed as having Neisseria gonorrhoeae infection.
- If laboratory tests for *C. trachomatis* are not available, the patient shows clinical signs of *Chlamydia* infection.

The regimen for the treatment of non-specific genital infections caused by *Chlamydia* is to use [18]:

- Doxycycline 2 x 100 mg per day orally, for 7 days OR.
- Azithromycin 1 g orally as a single dose OR.
- Tetracyclines 4 x 500 mg per day orally, for 7 days OR.
- Erythromycin 4 x 500 mg per day orally, for 7 days.

The treatment is in accordance with the guidelines issued by the CDC-MMWR in 2015 regarding the management of *Chlamydia* infection, which is as stated below [8].

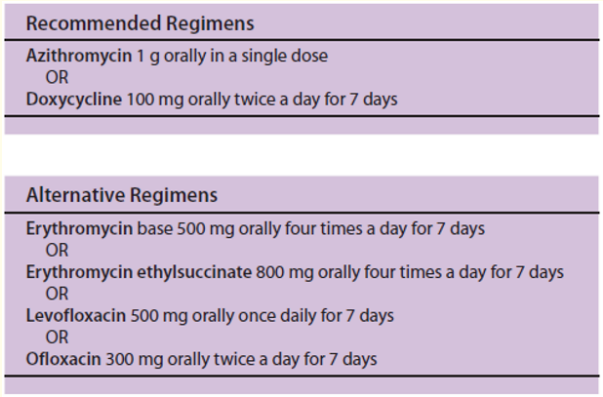

Figure 2: Guidelines for the therapy of Chlamydia infection according to the CDC - MMWR [18].

A test-of-cure culture (repeat testing after completion of therapy) to detect therapeutic failure ensures treatment effectiveness.

Therefore, this culture with should be obtained at a follow-up visit approximately 2 weeks after treatment is completed [18].

Conclusion

Sexual abuse must be considered a cause of Chlamydial infection in infants and children. However, perinatally transmitted *C. trachomatis* infection of the nasopharynx, urogenital tract and rectum might persist for 2 - 3 years.

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