Chapter

Chlamydial Infection

Dimitra Metallinou, Christina Nanou, Antigoni Sarantaki, Eleftheria Lazarou, Anastasia Liagkou and Katerina Lykeridou

Abstract

Chlamydial infection is one of the most common sexually transmitted infections worldwide, showing no decreasing trends in the incidence the last years. As a result, it presents a major burden of disease that impacts negatively people's sexual and reproductive health and may result in adverse perinatal outcomes. The aim of the chapter is to offer today's practitioners trustworthy guidance on the latest data in chlamydial infection. Thorough, up-to-date content on the epidemiology, pathophysiology, risk factors, clinical manifestations, diagnosis, treatment, prevention, prognosis and outcomes of infected infants, is presented. Data in children and adolescents that differ from infants, are also discussed. The chapter is organized consistently in order to help readers find information quickly and easily and thus, provide direct, optimal and evidence-based care to every pediatric patient.

Keywords: *Chlamydia trachomatis*, chlamydial infection, conjunctivitis, pneumonia, infant, children, adolescents

1. Introduction

More than 1 million sexually transmitted infections are acquired every day worldwide and chlamydial infection is the most common in the developed world, showing no decreasing trends in the incidence the last years [1]. As a result, chlamydial infection presents a major burden of disease that impacts negatively people's sexual and reproductive health and may result in adverse perinatal outcomes. As chlamydiae are largely asymptomatic and high rates of antibiotic resistance [2] have been shown, screening and treatment are the most crucial issues to reduce their impact globally.

Chlamydial infection can be transmitted to the infant during childbirth, resulting in conjunctivitis or pneumonia as a clinical disease. If present beyond the neonatal period in a child, may be a sign of sexual abuse. Sexually transmitted infection can occur in sexually active adolescents leading to a cascade of potentially serious inflammatory-induced sequelae.

2. Definition - background

"Chlamydiae", originate from the Greek word "chlamyda", meaning "cloak". They are Gram-negative obligate intracellular bacteria pathogenic to humans or animals and mainly transmitted through direct contact with infected tissue,

including vaginal, anal or oral sex and can even be passed from an infected mother to the newborn during childbirth. Some species though, pathogenic to animals can be transmitted to humans also [3].

Chlamydiae have a unique biphasic developmental cycle which involves transition between two major morphologic forms: (1) the infectious forms, called elementary bodies convert into (2) non-infectious, reproductive forms, called reticulate bodies. This transition takes place within the host cell and differentiates the metabolically inactive elementary body into the metabolically active reticulate body. The reticulate body contains no cell wall and is detected as an inclusion in the cell. Chlamydiae contain DNA, RNA and ribosomes [4, 5].

There are four recognized species of Chlamydiae: Chlamydia trachomatis, Chlamydia psittaci, Chlamydia pneumoniae, and Chlamydia pecorum. Humans are the only natural host for *Chlamydia trachomatis (C. trachomatis)*. This bacterium has a distinct developmental cycle, approximately 48–72 hours, which only replicates inside eukaryotic host cells. It uses energy phosphate compounds from the host cell during its growth and replication [6]. Preferentially infects squamo-columnar epithelial cells of the eye and the genital tract. Its genome size is 1000 kB [7].

3. Pathophysiology

Although infection by C. trachomatis is a major sexually transmitted genital infection globally, eye infections may be also spread by personal contact and contaminated items which are touched or held by hands, such as towels, in areas with poor sanitation [8]. Repeated and chronic infections, usually in developing countries, can lead to trachoma, which is a chronic follicular keratoconjunctivitis that causes scarring and neovascularization of the cornea that can result in blindness [9].

In women, genital tract infections with by C. trachomatis are usually asymptomatic and that is why it is frequently characterized as the "silent epidemic" [10]. If left untreated though, it can lead to serious sequelae, including urethritis, bartholinitis, mucopurulent cervicitis, endometritis, salpigitis, and pelvic inflammatory disease which may subsequently compromise fertility or predispose to ectopic pregnancy. Additionally, several pregnancy complications have been linked to chlamydial infection, including chorioamnionitis, premature rupture of membranes, preterm labour and birth, low birth weight, intrauterine growth restriction and postpartum endometritis [11–15]. In males, (or men) may cause epididymitis, proctitis, prostatitis, urethritis and reactive arthritis [16].

In infants, C. trachomatis can cause conjunctivitis and/or pneumonia. More rarely, C. trachomatis occurs also in the vagina, urethra and rectum. Occasional C. trachomatis infection in children and adolescents (with no prior sexual activity) should be seen in the context of sexual abuse, especially when Chlamydiae are detected in the anorectal or genital region [17].

There are 18 serotypes of C. trachomatis. The genital strains belong to one of the serotypes D through K while trachoma strains to the serotypes A through C [18]. The most common genotype among infants is type E [19, 20].

4. Prevalence

Based on prevalence data from 2009 to 2016, the estimated pooled global prevalence of chlamydial urogenital infection in women and men, aged 15–49 years,

was 3.8% and 2.7%, respectively [21]. Rates of infection among adolescent girls exceed 20% in many urban populations, but can be as high as 15% in suburban populations [22].

Worldwide, the prevalence of C. trachomatis in pregnant women varies from 1.0%–36.8%, while in high income countries it is estimated from 3%–14% [23]. Especially in European western countries, the prevalence of genital C. trachomatis infection in pregnant women based on nucleic acid amplification tests (NAAT) from either first void urine or a vaginal and/or endocervical swab, ranges from 3% to 6% [24]. However, prevalence may vary significantly during pregnancy among different continents [23] (**Figure 1**).

Approximately 50%–70% of infants exposed to an infected mother's genital flora during vaginal birth, will acquire chlamydia infection if no prophylaxis is given before or just after birth. More specifically, the 10%–20% of all infected infants will develop pneumonia and the 30%–50% conjunctivitis. Prevalence data of neonatal chlamydial conjunctivitis and pneumonia from several regions [25] are summarized in **Figure 2**.

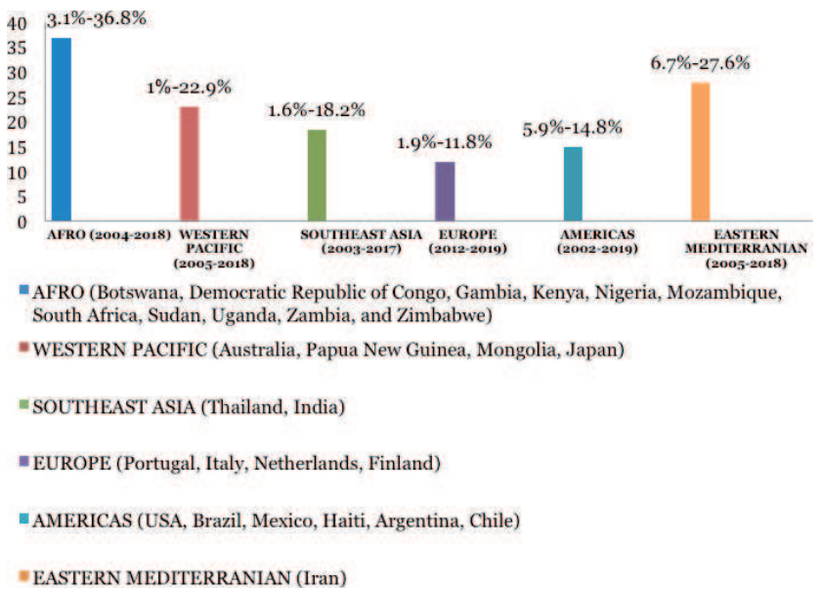

Figure 1.
Prevalence of C. trachomatis infection in pregnant women across all continents.

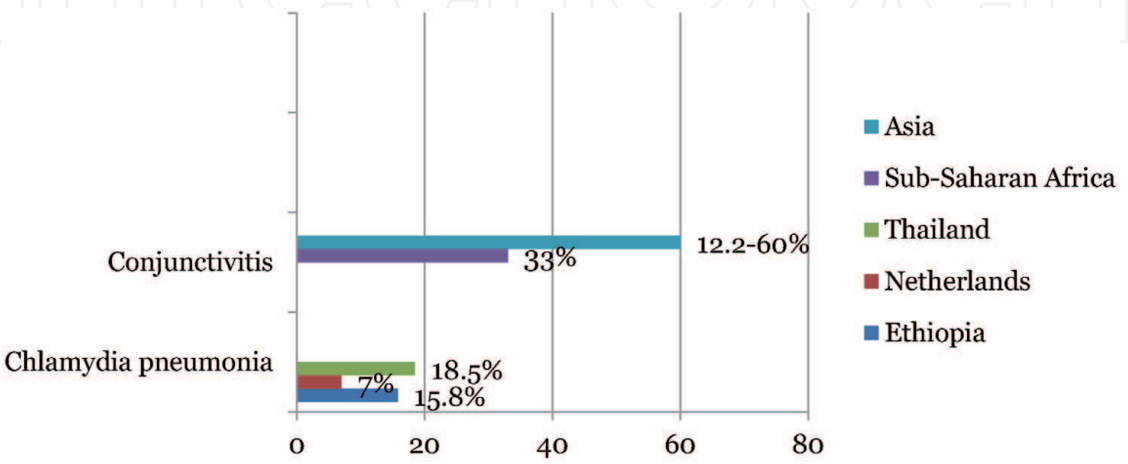

Figure 2.
Prevalence of chlamydial conjunctivitis and pneumonia in infants.

5. Risk factors

It seems that young women (<25 years old) are more prone to chlamydial infection due to anatomic differences in the cervix, such as cervical ectropion [16, 26]. In this condition, the glandular cells that line the endocervix are present on the ectocervix, leading to exposure of the glandular cells to the vaginal milieu and C. trachomatis has a preference for the glandular epithelium [5, 27].

Other factors associated with an increased risk of infection are numerous sexual partners, sexual intercourse with non-condom use, absence of barrier contraceptives, use of oral contraceptives, partner with concurrent partners or sexually-transmitted disease or non-gonococcal urethritis, non-gonococcal mucopurulent cervititis, sterile pyuria, other sexually transmitted diseases, unmarried status, nulliparity, African/American/Hispanic ethnicity and poor socio-economic condition [5, 23, 28].

Regarding infants, the main risk factor is vertical transmission (mother-to-child) after vaginal birth. Transmission after a cesarean section is unusual, unless premature rupture of the membranes of an infected mother is reported.

6. Clinical presentation

6.1 Conjunctivitis

Neonates exposed to C. trachomatis in an infected birth canal may develop conjunctivitis, sometimes referred to as "ophthalmia neonatorum", with transmission rate from 30%–50% [25]. Neonatal conjunctivitis caused by C. trachomatis has been reported as the most common infectious cause of neonatal conjunctivitis worldwide.

Conjunctivitis typically occurs between 5–14 days after delivery and can be unilateral or bilateral. It has a variety of clinical presentations in the infant. It is characterized by palpebral erythema and oedema, as well as eye discharge. Initially, the eye discharge is watery and later becomes purulent and copious. Moderate eye drainage and redness is common. Corneal opacification, chemosis and pseudomembranes may be present. Topical prophylaxis with erythromycin does not prevent but reduces the incidence of the chlamydial conjunctivitis [29–31].

Moreover, the 10%–20% of the infants with chlamydial conjunctivitis will develop pneumonia [25].

6.2 Pneumonia

The species C. psittaci, C. trachomatis and C. pneumoniae can all cause pneumonia in humans. Perinatal transmission of C. trachomatis has been reported to cause neonatal pneumonia with potentially a life-threatening severity. Usual age of presentation is at 3 weeks to 3 months of life [32]. In half of the cases concurrent or previous conjunctivitis is present and in one third of the cases otitis media is co-existing [33]. When C. pneumoniae is the cause, infection is predominantly asymptomatic or mild but can result in the development of acute upper and lower respiratory illness [34].

Upper and lower respiratory tracts may be directly infected intrapartum. C. trachomatis, which is the most common though, has been documented to be pathogen causing lower respiratory tract infection in children less than 6 months of age. Infants may present moderate symptoms, such as rhinitis, mucoid rhinorrhea together with cough and increased respiratory rate for 3 or more weeks before

pneumonia. Most cases are afebrile. When pneumonia occurs, tachypnea, nasal obstruction and/or discharge, interstitial and peribronchiolar inflammation may exist, leading to significant morbidity manifested as low grade fever and paroxysmal staccato cough. Crepitant inspiratory rales often are heard on auscultation of the lungs, in contrast with expiratory wheezes which are distinctly uncommon. Hyperinflation of the lungs usually accompanies the diffused infiltrates observed on chest X-rays. Reticulonodular patterns and atelectasis have also been described. Eosinophilia may be also present [33, 35, 36].

In premature infants chlamydial pneumonia can be more serious. In the beginning, respiratory distress is observed which is followed later by worsening respiratory signs [37]. Apnea spells and respiratory failure may present as well [33, 38]. If chlamydial pneumonia is left untreated, infants are at high risk of developing later pulmonary dysfunction and possibly chronic respiratory disease, including mild to severe asthma [36]. Prophylaxis does not eliminate nasopharyngeal colonization or pneumonia.

It should be taken into consideration that C. trachomatis and C. pneumoniae are agents associated with community-acquired pneumonia in children and adolescents. They have not been associated with specific clinical syndromes among children and adolescents. Nevertheless, pharyngitis, bronchitis, and sinusitis may be present [38, 39].

6.3 Other clinical presentations in children and adolescents

In prepubertal girls, vaginitis may present, while in postpubertal girls, urethritis, bartholinitis, cervicitis, endometritis, salpingitis, proctitis, perihepatitis, are possible manifestations of the disease. Long-lasting infections may result in ectopic pregnancy, infertility or pelvic inflammatory disease [11, 13, 35]. In males, chlamydial infection may cause epididymitis, proctitis, prostatitis, urethritis and reactive arthritis. Lymphogranuloma venereum is extremely rare in children and adolescents below the age of 18 years old and is usually confined to HIV positive and homosexual men [35, 40].

Repeated and chronic chlamydial infection that affects eyes can lead to trachoma, a chronic follicular keratoconjunctivitis that causes scarring and neovascularization of the cornea and can even result in irreversible blindness [9]. It can be spread through contact with the eyes, eyelids, nose or throat secretions of infected people. Chlamydiae can be transmitted by contaminated handkerchiefs, towels, clothes or bed linen as well. Signs and symptoms of trachoma usually affect both eyes and may include: mild itching and irritation of the eyes and eyelids, eye discharge containing mucus or pus, eyelid swelling, light sensitivity (photophobia), eye pain, eye redness and vision loss. In areas where trachoma is endemic, usually poor and rural, active (inflammatory) trachoma is common among preschool-aged children, with prevalence rates which can be as high as 60–90% [8, 41].

7. Diagnosis

7.1 Laboratory studies

7.1.1 Tissue culture

For conjunctival specimens, any purulent exudate should be removed before collecting epithelial cells by rubbing a dry swab over the everted palpebral conjunctiva. The conjunctivae are often friable and may bleed after swabbing so great

attention is needed. For suspected pneumonia, material should be obtained from nasopharyngeal aspiration or deep suctioning of the trachea.

Culture of the bacterium is considered as the gold standard for diagnosing neonatal conjunctivitis and pneumonia. Proficiency in specimen collection and transport is paramount to accuracy in diagnostic testing for Chlamydiae [5, 42]. Both the sensitivity and the specificity of culture is nearly 100% but is directly related to the adequacy of the specimen. For optimal isolation of the bacteria, specimens should be refrigerated immediately after collection at 2 to 8 °C and kept at this temperature during transport to the laboratory. The intervening period between collection and laboratory processing of specimens should ideally not exceed the 48 hours [42].

7.1.2 Nucleic acid amplification test (NAAT)

This method amplifies the nucleic acid sequences of chlamydiae. Non-viable bacteria can be detected contrary to cell culture. All relevant clinical materials can be analyzed by NAATs, including urethral, cervical, vulvo-vaginal, anorectal and ocular swabs, first void urine, sperm or tissues [43]. The test is recommended for routine use in adults and older children but data relating to infants are insufficient. The NAATs have not been approved by the US Food and Drug Administration (FDA) for testing of conjunctival specimens from infants with suspected C. trachomatis conjunctivitis or for testing of nasopharyngeal swab, tracheal aspirate or lung biopsy specimens from infants with suspected C. trachomatis pneumonia [33, 35].

7.1.3 Antigen detection tests

Antigen tests based on the detection of either chlamydial lipopolysaccharides (enzyme immunoassay, EIA) or direct fluorescent antibodies (DFA) have also been found to perform relatively well when used with conjunctival specimens. Sensitivity of nasopharyngeal samples is poor. Antigen tests are no longer recommended for chlamydia testing in infants due to insufficient diagnostic accuracy [43].

7.1.4 Serum anti-chlamydial antibody concentration

Chlamydial IgG antibodies detected from infants during the first months of life reflect maternally transferred antibodies and correlate with the levels of maternal serum antibodies. Maternal IgG antibodies do not protect infants from developing chlamydial infection and infants born to antibody positive mothers usually lose their maternally transferred IgG-antibodies by nine months of age [24]. In infants with chlamydial pneumonia a microimmunofluorescence serum titer of ≥1:32 is considered diagnostic for infection [31, 33]. The IgM antibodies have been observed to develop as early as five days after infection and to persist for three months. Their determination is difficult and availability limited [24].

7.1.5 Other tests

Obtaining lung biopsies is not a routine practise for confirming chlamydial pneumonia, since the course of the disease is rarely fatal, but when a biopsy is obtained the material should be examined for chlamydiae [44]. Additionally in pneumonia, eosinophilia in the peripheral blood is usual with white blood cell count being normal. Blood gas measurements reveal mild to moderate hypoxemia [33, 35, 36].

7.2 Imaging

In cases of chlamydial pneumonia, the most chest radiographs show bilateral hyperexpansion and diffuse infiltrates with a variety of radiographic patterns, including interstitial, reticular nodular, atelectasis, coalescence and bronchopneumonia. Pleural effusion and lobar consolidates are usually absent [33, 45]. Radiological findings alone are non-specific so it is almost impossible to determine by radiographic manifestations that a specie of clamydiae is the causative organism of the pneumonia.

8. Treatment

8.1 Conjunctivitis

Oral erythromycin base or ethylsuccinate is a usual treatment for conjunctivitis in the infant, although erythromycin has been reported as risk factor for infantile hypertrophic pyloric stenosis when administered the first 2 weeks of life. Thus, parents and physicians should observe infants closely for any signs of intestinal obstruction. Azithromycin is an acceptable alternative [30, 33, 35] which is also recommended by WHO in neonates with chlamydial conjunctivitis [46]. Dosages in the most preferable treatments are:

- Oral erythromycin 50 mg/kg/day in 4 divided doses for 14 days **or**
- Oral azithromycin 20 mg/kg/day for 3 days

8.2 Pneumonia

For children, the following regimens can be used for respiratory infection due to C. trachomatis and C. pneumoniae [47]:

Preferred therapy **intravenously**

- azithromycin 10 mg/kg on days 1 and 2 of therapy; transition to oral therapy if possible

Accepted alternatives are:

- erythromycin lactobionate 20 mg/kg/day every 6 hours
- levofloxacin 16–20 mg/kg/day in 2 doses for children 6 months to 5 years old and 8–10 mg/kg/day once daily for children 5 to 16 years old; maximum daily dose should not exceed the 750 mg

Preferred therapy **orally** [47, 48].

- azithromycin 10 mg/kg/once on day 1, followed by 5 mg/kg/day once daily for 2–5 days

Accepted alternatives are:

- clarithromycin 15 mg/kg/day for 10 days
- erythromycin 50 mg/kg/day for 10–14 days

- doxycycline 2–4 mg/kg/day in 2 doses for children with age greater than 7 years old

- levofloxacin 500 mg once daily or moxifloxacin 400 mg once daily for adolescents with skeletal maturity

Antibiotic resistance may diminish the overall efficacy of antibiotics, thus, it is strongly advised to follow-up patients to determine whether initial treatment was effective [33, 35, 39]. Clarithromycin is therapeutically equivalent to other antibiotics studied and is associated with a better bacteriological eradication and a lower risk for related adverse events in children [49]. In general, no isolation measures are necessary. Parents or mother and her sexual partner should be evaluated and treated if needed.

8.3 Uncomplicated genital chlamydial infection

For adolescents with uncomplicated genital chlamydial infection, guidelines relating to sexually transmitted diseases by WHO [46] suggest one of the following options:

- oral azithromycin 1 g as a single dose

- oral doxycycline 100 mg twice a day for 7 days

or one of the following alternatives:

- oral tetracycline 500 mg four times a day for 7 days

- oral erythromycin 500 mg twice a day for 7 days

- oral ofloxacin 200–400 mg twice a day for 7 days

Children with body weight < 45 kg, the recommended regimen is [35]:

- oral erythromycin base or ethylsuccinate, 50 mg/kg/day, divided into 4 doses daily for 14 days.

Children with body weight > 45 kg and age < 8 years old, the recommended regimen is [35]:

- oral azithromycin 1 g in a single dose

For children 8 years old and older, the recommended regimens are [35]:

- oral azithromycin 1 g in a single dose **or**

- oral doxycycline 100 mg twice a day for 7 days

8.4 Lymphogranuloma venereum (LGV)

In adolescents with LGV, it is suggested by WHO [46] the administration of doxycycline 100 mg orally twice daily for 21 days over azithromycin 1 g orally, weekly for 3 weeks.

9. Prevention

The most effective method of controlling perinatal chlamydial infection appears to be screening and treatment of pregnant women. The U.S. Centers for Disease Control and Prevention (CDC) recommend that "all pregnant women aged <25 years and older women at increased risk for infection should be routinely screened for C. trachomatis at the first prenatal visit and be retested during the third trimester to prevent maternal postnatal complications and chlamydial infection in the neonate" [44]. Healthcare professionals must cooperate closely to identify early the high-risk populations, educate and counsel the patients about sexual health and importance of screening and completing treatment.

According to recommendation of WHO [46], all neonates should be offered immediately after birth topical ocular prophylaxis to both eyes for the prevention of gonococcal and chlamydial ophthalmia neonatorum with one of the following options:

- tetracycline hydrochloride 1% eye ointment
- erythromycin 0.5% eye ointment
- povidone iodine 2.5% solution (water-based)
- silver nitrate 1% solution
- chloramphenicol 1% eye ointment

No vaccine is currently available for either trachoma or chlamydial genital infections. However, a first-in-human, randomized, double-blind, placebo-controlled, phase 1 trial was conducted between 2016–2017 to assess safety and immunogenicity of a chlamydial vaccine candidate [50].

As far as trachoma is concerned, a WHO-recommended elimination strategy summarized by the acronym"SAFE", is being implemented in endemic countries [41]. This consists of:

Surgery to treat the blinding stage.
Antibiotics to clear infection.
Facial cleanliness and.
Environmental improvement.

10. Prognosis

If proper treatment starts early, chlamydial infection should resolve without complications and with good prognosis, overall. Patients with mild symptoms usually recover within 7–10 days after initiation of the treatment. Dry cough and general weakness can persist after the disease, slowing complete remission from 1 week to 2 months. If neglected, serious complications may develop which can even lead to mortality [36].

11. Conclusion

Chlamydial infection is a significant worldwide public health problem, affecting both general and special populations. Early identification and management of

high risk populations, with defined strategies, will eliminate crucially the burden of chlamydial infection. Obstetricians, gynecologists, midwives and pediatricians/neonatologists should be educated up-to-date and offered trustworthy guidance on the latest data in chlamydial infection. By applying scientific knowledge in clinical practice, these professionals can provide direct, optimal and evidence-based care to every pediatric patient.

Conflict of interest

The authors declare no conflict of interest.

Author details

Dimitra Metallinou[1*], Christina Nanou[1], Antigoni Sarantaki[1], Eleftheria Lazarou[2], Anastasia Liagkou[3] and Katerina Lykeridou[1]

1 Department of Midwifery, Faculty of Health and Care Sciences, University of West Attica, Athens, Greece

2 Iasis Private Hospital Paphos, Paphos, Cyprus

3 General Maternity and Gynecology Clinic"IASO," Athens, Greece

*Address all correspondence to: metallinoudimitra@gmail.com

References

[1] World Health Organization. Sexually transmitted infections (STIs) [Internet]. 2019. Available from: https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis) [Accessed 2021-01-30]

[2] Sandoz KM, Rockey DD. Antibiotic resistance in Chlamydiae.Future Microbiol. 2010;5(9):1427-1442. doi:10.2217/fmb.10.96

[3] Elwell C, Mirrashidi K, Engel J. Chlamydia cell biology and pathogenesis. Nat Rev Microbiol. 2016;14(6):385-400. doi:10.1038/nrmicro.2016.30

[4] Becker Y. Chlamydia. In: Baron S, editor. Medical Microbiology. 4th ed. Galveston (TX): University of Texas Medical Branch at Galveston; 1996.

[5] Malhotra M, Sood S, Mukherjee A, Muralidhar S, Bala M. Genital Chlamydia trachomatis: an update. Indian J Med Res. 2013;138(3):303-316

[6] Bastidas RJ, Elwell CA, Engel JN, Valdivia RH. Chlamydial intracellular survival strategies. Cold Spring Harb Perspect Med. 2013;3(5):a010256. Published 2013 May 1. doi:10.1101/cshperspect.a010256

[7] Stephens RS, Kalman S, Lammel C, et al. Genome sequence of an obligate intracellular pathogen of humans: Chlamydia trachomatis. Science. 1998;282(5389):754-759. doi:10.1126/science.282.5389.754

[8] Satpathy G, Behera HS, Ahmed NH. Chlamydial eye infections: Current perspectives. Indian J Ophthalmol. 2017;65(2):97-102. doi:10.4103/ijo.IJO_870_16

[9] Ubani U. Trachoma and Inclusion Conjunctivitis, Common Eye Infections. In: Chaudhry I, editor. Common eye infections. IntechOpen; 2013. doi: 10.5772/53861. Available from: https://www.intechopen.com/books/common-eye infections/trachoma-and-inclusion-conjunctivitis

[10] Okoror LE, Agbonlahor DE, Esumeh FI, Umolu PI. Prevalence of chlamydia in patients attending gynecological clinics in south eastern Nigeria. Afr Health Sci. 2007;7(1):18-24. doi:10.5555/afhs.2007.7.1.18

[11] Tsevat DG, Wiesenfeld HC, Parks C, Peipert JF. Sexually transmitted diseases and infertility. Am J Obstet Gynecol. 2017;216(1):1-9. doi:10.1016/j.ajog.2016.08.008

[12] Kacerovsky M, Romero R, Pliskova L, et al. Presence of Chlamydia trachomatis DNA in the amniotic fluid in women with preterm prelabor rupture of membranes [published online ahead of print, 2019 Jul 15]. J Matern Fetal Neonatal Med. 2019;1-12. doi:10.1080/14767058.2019.1640676

[13] Hussen S, Wachamo D, Yohannes Z, Tadesse E. Prevalence of chlamydia trachomatis infection among reproductive age women in sub Saharan Africa: a systematic review and meta-analysis. BMC Infect Dis. 2018;18(1):596. Published 2018 Nov 26. doi:10.1186/s12879-018-3477-y

[14] Menon S, Timms P, Allan JA, et al. Human and Pathogen Factors Associated with Chlamydia trachomatis-Related Infertility in Women. Clin Microbiol Rev. 2015;28(4):969-985. doi:10.1128/CMR.00035-15

[15] Cluver C, Novikova N, Eriksson DO, Bengtsson K, Lingman GK. Interventions for treating genital Chlamydia trachomatis infection in pregnancy. Cochrane Database Syst Rev. 2017;9(9):CD010485. Published

2017 Sep 22. doi:10.1002/14651858.CD010485.pub2

[16] Mohseni M, Sung S, Takov V. Chlamydia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537286/

[17] Hammerschlag MR, Guillén CD. Medical and legal implications of testing for sexually transmitted infections in children. Clin Microbiol Rev. 2010;23(3):493-506. doi:10.1128/CMR.00024-09

[18] Vaulet LG, Entrocassi C, Corominas AI. et al. Distribution study of Chlamydia trachomatis genotypes in symptomatic patients in Buenos Aires, Argentina: association between genotype E and neonatal conjunctivitis. BMC Res Notes 3, 34. 2010. doi.org/10.1186/1756-0500-3-34

[19] Li Y, Xiong L, Huang Y, et al. The clinical characteristics and genotype distribution of Chlamydia trachomatis infection in infants less than six months of age hospitalized with pneumonia. Infect Genet Evol. 2015;29:48-52. doi:10.1016/j.meegid.2014.11.004

[20] Balla E, Petrovay F, Erdősi T, et al. Distribution of Chlamydia trachomatis genotypes in neonatal conjunctivitis in Hungary. J Med Microbiol. 2017;66(7):915-918. doi:10.1099/jmm.0.000523

[21] Rowley J, Vander Hoorn S, Korenromp E, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. Bull World Health Organ. 2019;97(8):548-562P. doi:10.2471/BLT.18.228486

[22] Hammerschlag M. Genital tract infections. In: Kliegman R, Stanton B, Geme J, Schor N, editors. Nelson textbook of pediatrics. 20th ed. Elsevier; 2016. p 1494

[23] Olaleye AO, Babah OA, Osuagwu CS, Ogunsola FT, Afolabi BB. Sexually transmitted infections in pregnancy – An update on Chlamydia trachomatis and Neisseria gonorrhoeae. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2020;255: 1-12. doi:10.1016/j.ejogrb.2020.10.002.

[24] Honkila M. Chlamydia trachomatis infections in neonates and infants [thesis]. University of Oulu, Faculty of Medicine; 2018

[25] Adachi K, Nielsen-Saines K, Klausner JD. Chlamydia trachomatis Infection in Pregnancy: The Global Challenge of Preventing Adverse Pregnancy and Infant Outcomes in Sub-Saharan Africa and Asia. BioMed Research International, 2016; 9315757: 1-21. doi:10.1155/2016/9315757

[26] Lee V, Tobin JM, Foley E. Relationship of cervical ectopy to chlamydia infection in young women. J Fam Plann Reprod Health Care. 2006;32(2):104-106. doi:10.1783/147118906776276440

[27] Aggarwal P, Ben Amor A. Cervical Ectropion. In: StatPearls. Treasure Island (FL): StatPearls Publishing; November 17, 2020.

[28] Tiller CM. Chlamydia during Pregnancy: Implications and Impact on Perinatal and Neonatal Outcomes. Journal of Obstetric, Gynecologic & Neonatal Nursing. 2002; 31(1): 93-98. doi:10.1111/j.1552-6909.2002.tb00027.x.

[29] Makker K, Nassar GN, Kaufman EJ. Neonatal Conjunctivitis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441840/

[30] Zikic A., Schünemann H., Wi Teodora, et al, Treatment of Neonatal Chlamydial Conjuctivitis: A Systemic Review and Meta-analysis, J Pediatric Infect Dis Soc,2018;7(3):e107-e115

[31] Darville T., Chlamydia trachomatis Infections in Neonates and Young Children, Seminars in Pediatric Infectious Diseases, 2005;16(4), 235-244

[32] Mishra KN, Bhardwaj P, Mishra A, Kaushik A. Acute Chlamydia trachomatis respiratory infection in infants. J Glob Infect Dis. 2011;3(3):216-220. doi:10.4103/0974-777X.83525

[33] Gomella T. Neonatology. 7th ed. McGraw Hill Education; 2013. p581–p583

[34] Porritt RA, Crother TR. Chlamydia pneumoniae Infection and Inflammatory Diseases. For Immunopathol Dis Therap. 2016;7(3-4):237-254. doi:10.1615/ForumImmunDisTher.2017020161

[35] American Academy of Pediatrics. Chlamydial infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red Book: 2015 Report of the Committee on Infectious Diseases. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2015:288-94

[36] Gautam J, Krawiec C. Chlamydia Pneumonia. [Updated 2020 Dec 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560874/

[37] Bekler C, Kultursay N, Ozacar T, Sayiner A, Yalaz M, Akisu M. Chlamydial infections in term and preterm neonates. Jpn J Infect Dis. 2012;65(1):1-6.

[38] Davies HD. Community-acquired pneumonia in children. Paediatr Child Health. 2003;8(10):616-619. doi:10.1093/pch/8.10.616

[39] Leung AKC, Wong AHC, Hon KL. Community-Acquired Pneumonia in Children. Recent Pat Inflamm Allergy Drug Discov. 2018;12(2):136-144. doi:10.2174/1872213X12666180621163821

[40] Cole MJ, Field N, Pitt R, et al. Substantial underdiagnosis of lymphogranuloma venereum in men who have sex with men in Europe: preliminary findings from a multicentre surveillance pilot. Sex Transm Infect. 2020;96(2):137-142. doi:10.1136/sextrans-2019-053972

[41] World Health Organization. Trachoma. Fact sheet [Internet]. 2020. Available from: https://www.who.int/news-room/fact-sheets/detail/trachoma [Accessed 2021-01-30]

[42] Watson EJ, Templeton A, Russell I, et al. The accuracy and efficacy of screening tests for Chlamydia trachomatis: a systematic review. J Med Microbiol. 2002;51(12):1021-1031. doi:10.1099/0022-1317-51-12-1021

[43] Meyer T. Diagnostic Procedures to Detect Chlamydia trachomatis Infections. Microorganisms. 2016;4(3):25. Published 2016 Aug 5. doi:10.3390/microorganisms4030025

[44] Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines [Internet]. 2015. Available from: https://www.cdc.gov/std/tg2015/chlamydia.htm. [Accessed 2012-01-31]

[45] Radkowski MA, Kranzler JK, Beem MO, Tipple MA. Chlamydia pneumonia in infants: radiography in 125 cases. AJR Am J Roentgenol. 1981;137(4):703-706. doi:10.2214/ajr.137.4.703

[46] World Health Organization. Guidelines for the Treatment of

Chlamydia trachomatis. Geneva; 2016 [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK379708/ [Accessed 2021-01-31]

[47] Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis. 2011;53(7):e25-e76. doi:10.1093/cid/cir531

[48] Kohlhoff SA, Hammerschlag MR. Treatment of Chlamydial infections: 2014 update. Expert Opin Pharmacother. 2015;16(2):205-212. doi:10.1517/14656566.2015.999041

[49] Gutiérrez-Castrellón P, Mayorga-Buitron JL, Bosch-Canto V et al. Efficacy and safety of clarithromycin in pediatric patients with upper respiratory infections: a systematic review with meta-analysis. Rev Invest Clin. 2012;64(2):126-135.

[50] Abraham S, Juel HB, Bang P, et al. Safety and immunogenicity of the chlamydia vaccine candidate CTH522 adjuvanted with CAF01 liposomes or aluminium hydroxide: a first-in-human, randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Infect Dis. 2019;19(10):1091-1100. doi:10.1016/S1473-3099(19)30279-8