Review Article

Genital infections by Chlamydia trachomatis-An overview

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Abstract:

Genital infections by Chlamydia trachomatis are now recognized as highly prevalent sexually transmissible disease. In frequency, they surpass the classic sexually transmissible diseases such as syphilis and gonorrhea and thus constitute a serious public health problem. Chlamydia trachomatis is an obligate intracellular gram negative bacterium which have a unique growth cycle and are placed in their own family (Chlamydiae).Chlamydia trachomatis is now one of the most Prevalent bacteria found in classic sexually transmissible disease and as such constitutes a serious Public heath problem. World Heath Organization (WHO) estimated that 92 million new chlamydial infections occur worldwide annually affecting more women (50 Million) then men (42million). And highest chlamydial infected population were in south and South-east Asia (43million) then sub-Saharan Africa (16million)(WHO 2001).This review article is a discussion on history, epidemiology, pathogenesis, clinical features, diagnosis and modern trend of treatment, prevention of Chlamydial infections in age group. Effective delivery of prevention messages requires client-centered counseling and education regarding specific actions that can reduce the risk for chlamydia transmission e.g., abstinence, condom use, limiting the number of sex partners, modifying sexual behaviors and vaccination.

Key words: *Chlamydia trachomatis,World Heath Organization (WHO,) treatment, prevention.*

Introduction

Genital infections by Chlamydia trachomatis are now recognized as highly prevalent sexually transmissible disease. In frequency, they surpass the classic sexually transmissible diseases such as syphilis and gonorrhea and thus constitute a serious public health problem[1].Chlamydia trachomatis is an obligate intracellular gram negative bacterium which have a unique growth cycle and are placed in their own family (Chlamydiae). Among three Chlamydia species Chlamydia trachomatis have serological variants of which serovars A-C of C. trachomatis preferably colonise the eye and cause trachoma, serovars D-K preferably colonise the genital tract and cause genital infections and L1-L3 cause lymphogranuloma venereum. C. trachomatis strains have an extrachromosomal plasmid, which was sequenced to be a 7493-base pair plasmid. The plasmid of C. trachomatis is a favored target for DNA-based diagnosis of C. trachomatis because there are approximately 7-10 copies of the plasmid present per chlamydial particle. The Chlamydia organism expresses a major outer membrane protein (MOMP) that is surface-exposed. It is coded by the Omp 1 gene and used for genotype determinations of C. trachomatis.[2,3,4].

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Genital C. trachomatis infection is a sexually transmitted disease. Eighty percent of the women do not experience symptom. But those who develops symptoms after three weeks incubation period have dysuria, vaginal discharge, contact bleeding, poorly differentiated abdominal pain. Approximately 35-50% of non gonococcal urethritis is due to Chlamydia trachomatis. Upto 40% women with untreated chlamydial infection may develop PID and about 20% of these become infertile, 18% results in chronic pelvic pain. Women infected with Chlamydia trachomatis have 3-5 fold increased risk of acquiring HIV. Women infected by C. trachomatis are prone to invasive cervical cancer .[5,6,7].

Historical background of Chlamydia trachomatis

Genital chlamydial infection is caused by the bacterium Chlamydia trachomatis. The Word 'Chlamys' is Greek for "cloak drapped around the shoulder". This describes how the intracytoplasmic inclusions caused by the bacterium are "draped" around the infected cells nucleus[8]. Trachoma, the chlamydial disease is among the human diseases recognized since antiquity, having been described in Ebers papyrus (1500BC). The name trachoma was first used by Discorides in 60 AD and the stages of the disease were described by Galen a century later. From the Middle Eastern reservoir, it spread throughout Europe in many waves from the time of the crusades to Napolean. It also is the disease from which Chlamydia were first demonstrated.[9].

Epidemiology

Chlamydia trachomatis is now one of the most prevalent bacteria found in classic sexually transmissible disease and as such constitutes a serious Public heath problem. World Heath Organization (WHO) estimated that 92 million new chlamydial infections occur worldwide annually affecting more women (50 Million) then men (42million). And highest chlamydial infected population were in south and South-east Asia (43million) then sub-Saharan Africa (16million).[10].

Chlamydial genital tract infections have a world wide distribution. Among the Sexually Transmitted Diseases (STDs), C.trachomatis infection is the most prevalent disease today. World Health Organisation (WHO) published a report in 2001 provides estimates of the extent of the world's STD epidemics in 1999. WHO reported that, around 92 million (27%) among 340 million new curable STDs (syphilis, gonorrhea, Chlamydia and trichomoniasis) were due to chlamydial infections. Estimated new cases of Chlamydia infections (in millions) among adults in 1999 were 3.93 (4.2%) in North America, 5.22 (5.6%) in Western Europe, 3.15 (3.4%) in North Africa and middle Europe, 5.97 (6.5%) in Eastern Europe & central Asia, 15.89 (17.2%) in Sub-Saharan Africa, 42.89 (46.6%) in South and South East Asia, 5.3 (5.7%) in East Asia and Pacific, 0.3 (0.3%) in Australia and New Zealand, 9.31 (10.1%) in Latin

Genome structure

Chlamydia trachomatis has a genome that consists of 1,042,519 nucleotide base pairs and has approximately 894 likely protein coding sequences. C. trachomatis strains have an extrachromosomal plasmid, which was sequenced to be a 7493-base pair plasmid. Because there is less than 1% nucleotide sequence variation, plasmids from human C. trachomatis isolates are considered to be very similar. All the isolates are about 7,500 nucleotides long and have eight open reading frames computer-predicted to code for proteins of more than 100 amino acids, with short non-coding sequences between some of them.

Interestingly, in their nucleotide sequence, chlamydial plasmids are more closely related than is the corresponding chromosomal DNA. The plasmid of C. trachomatis is a favored target for DNA-based diagnosis of C. trachomatis because there are approximately 7-10 copies of the plasmid present per chlamydial particle. Its sequence is highly conserved among different isolates of C. trachomatis. Some C. trachomatis strains lack these plasmids, and the consequences aid in detection of the plasmid free variant of C. trachomatis strain. Plaque purified C. trachomatis that do not contain the plasmids have unusual inclusion morphology, have no glycogen, and show no alteration in antibiotic sensitivity. However, the fact that existence of such strains shows that the plasmid is not essential for C. trachomatis survival .[11].

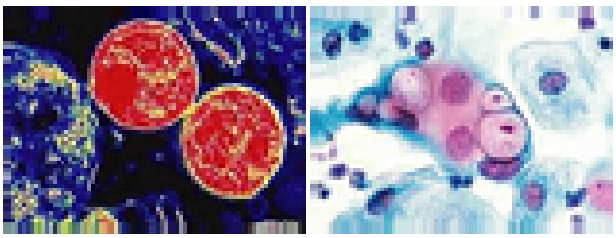


Fig: a. Chlamydia is the most common sexually transmitted infection
b. Pap smear showing C. trachomatis (H&E stain)

Growth cycle

Chlamydiae have a special preference for columnar epithelial cells. Once the Chlamydiae and host cell have come into contact, the organism enters the cell within a vesicle. Viable Chlamydiae entering the host cell cytoplasm inhibit fusion with lysosomal vesicles and so escape degradation.

In the vesicles the EB loses its dense DNA core. The cell wall becomes less rigid due to breaking of the disulphide bonds; the particle increases in size and becomes an RB. The RBs have no cytochrome and lack the ability to produce ATP, which must be supplied by the host. In the vesicle the RB divides by binary fission to yield pleomorphic organisms. At 18-20 h the DNA condenses, disulphide bonds are formed in the outer-membrane proteins and new EBs are generated within the endosomal vesicle (Smith 1998). By 40 hours after infections the reticulate bodies reorganize into elementary bodies forming the characteristic inclusion. At 48 hours after infection, the release of EBs follows autolysis of the host cell, leading to cell death and the release of infectious EBs, to begin a new cycle.[12]

The RB divides by binary fission resulting in 4-26 RBs within the vacuole in 8-12 hours. After 20 hours, if examined under electron microscope, a central condensation is noted within some of the particles and these are typical EBs resulting from the RBs. The inclusions within the cell increase in number and begin to displace the nucleus. After 48-60 hours approximately 100 or more EBs ruptures extracellularly to release the particles.[13]

The need of Chlamydiae for specific amino acids may lead to an inhibition of growth which can be reversed on the addition of the essential amino acid. This obviously gives the opportunity for latency since an amino acid-starved infection may lie dormant for a period but reappear on the addition of the essential building block

Clinical presentation:

Genital Chlamydia trachomatis is dangerous because 75% of women and 50% of men who are infected are asymptomatic, thus are unaware that they are infected. Prolonged exposure to the pathogen leads to infertility in both men and women. Infection also subjects women to pelvic inflammatory disease as well as ectopic pregnancy. Research has shown that women infected with Chlamydia have an increased risk for cervical cancer and HIV transmission (PNAS.org) In men, infections often begin in the urethra, with urethritis, and can progress to the upper genital tract, causing epididymitis and prostatitis. The bacterium can also attach to sperm, which decreases the sperms viability and motility, in turn reducing fertility. This attachment to the sperm also increases the chances of transmission to women.[14]

Symptoms in women include vaginal discharge, irritation of the pubic area, burning during urination, lower abdominal pain, painful intercourse, and vaginal bleeding. Men's symptoms usually include a clear, white, or yellow discharge from the urethra, burning sensation during urination, tenderness or pain in the testicles, and tingling or itching around the tip of the urethra. If symptoms do occur, they usually appear within 1 to 3 weeks after exposure.[15]

Laboratory Diagnosis:

Several laboratory methods are used for the diagnosis of Chlamydia trachomatis. Such as microscopic detection of inclutions by giemsa staining or iodine staining, Immunochromatographic test (ICT), Cell culture which is gold standard and laborious, Direct fluorescent antibody test (DFA), Enzyme linked immunosorbant assay (ELISA), DNA amplification polymerase chain reaction (PCR) and sequencing.

There are two strains of Chlamydia trachomatis :

Plasmid free strains.
Plasmid mutant strain.

Some studies suggest that plasmid free variant of Chlamydia trachomatis may on rare occasions be present in clinical samples and these will not be detected if the plasmid is used as target DNA.

Among the various laboratory methods for diagnosing C.trachomatis, Immunochromatographic method is rapid, simple, less time consuming technique. The assay does not require specialized equipment or extensive training and takes less than 30 minutes from sample to result. Based on culture the sensitivity of ICT was 88.9% and the specificity was 99% .[16]

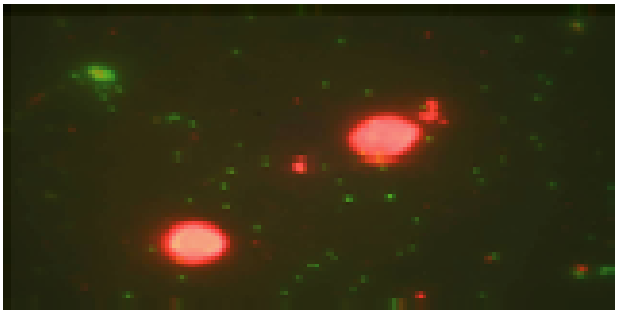
Molecular genetics techniques are useful for the identification of microorganisms that are difficult, such as C. trchomatis, and for those that grow slowly. PCR is more sensitive test than cell culture; it has a high

sensitivity and specificity when compared to other tests used for C. trchomatis diagnosis, such as direct immunofluorescence and ELISA, Which give some false-positive results (Santos C et al. 2003). DNA amplification techniques has resulted in assays which have sensitivities of greater than 90% and specificities approaching 100%. Polymerase chain reaction (PCR) has recently been introduced for detection of C trchomatis and studies have reported its superior sensitivity in comparison with culture, enzyme-linked immunosorbent assay or direct flurescein-conjugated antibody (DFA) staining.[17]

Currently, C. trachomatis is classified into 15 different serovars based on immunogenic epitope analysis of the major outermembrane protein (MOMP) with polyclonal and monoclonal antibodies . The MOMP is the principal immunodominant surface antigen of C. trachomatis, with antigenic determinants located across four symmetrically spaced variable domains (VDI to VDIV), which are flanked and interspaced by five constant domains. Variable domains are coded by the omp1 gene, and their nucleotide sequences exhibit distinct variations in different serovars. Subsequently, they have become widely used for the genotyping of C. trachomatis isolates. Typically, C. trachomatis serovars A through C are found associated with trachoma, serovars D through K are associated with urogenital infections, and serovars L1 through L3 are associated with the systemic disease lymphogranuloma venereum. Genotypic characterization of C. trachomatis isolates not only can provide valuable insight into the C. trachomatis serovars circulating within a given community but also can improve understanding of their epidemiology, which may assist in developing strategies for improved sexually transmitted disease (STD) control.[18]

Chlamydia trachomatis can be identified by a molecular technique like PCR. It can be done by plasmid based, MOMP based and ribosomal DNA based PCR. Plasmid based amplification was found to be 10 to 1000 times more sensitive then others.[19]

Figure 01: A positive direct fluorescent antibody test shows extracellular elementary bodies as apple green fluorescent pin point smooth edged disc shaped bodies (40X).



Treatment:

CDC alternative recommended treatment for uncomplicated chlamydial infections in non-pregnant adolescents and adults alternate regimens:

Erythromycin base 500 mg orally 4 times a day x 7 days
or
Erythromycin ethylsuccinate 800 mg orally 4 times a day x 7 days
or
Ofloxacin 300 mg orally twice a day x 7 days
Levofloxacin 500 mg orally once a day x 7 days

CDC recommended treatment for pregnant women recommended regimens:
Erythromycin base 500 mg orally 4 times a day x 7 days
or
Amoxicillin 500 mg orally 3 times a day x 7 days

Alternate regimens:
Erythromycin base 250 mg orally 4 times a day x 14 days
or
Erythromycin ethylsuccinate 800 mg orally 4 times a day x 7 days
or
Erythromycin ethylsuccinate 400 mg orally 4 times a day x 14 days
or
Azithromycin 1 g orally single dose
CDC RECOMMENDED TREATMENT FOR CHILDREN
CHILDREN < 45 kg
Erythromycin 50 mg/kg/day orally divided into 4 doses for 14 days

CHILDREN > 45 kg and < 8 Years of Age
Azithromycin 1 g orally single dose
CHILDREN ≥ 8 Years of Age
Azithromycin 1 g orally single dose
or
Doxycycline 100 mg orally twice a day x 7 days

CDC RECOMMENDED TREATMENT FOR NEONATAL INFECTIONS

Erythromycin* 50 mg/kg/day orally divided into 4 doses for 10-14 day
(CDC MMWR 2006)

Prevention Counseling:

Effective delivery of prevention messages requires client-centered counseling and education regarding specific actions that can reduce the risk for chlamydia transmission e.g., abstinence, condom use, limiting the number of sex partners, modifying sexual behaviors and vaccination. Prevention messages should be individually delivered and based on stages of patient development and understanding of sexual issues. Performing counseling and discussing behavioral interventions have been shown to reduce the likelihood of Chlamydia STD and reduce risky sexual behavior.[20,21,22]

Prevention Methods

Client-initiated interventions to reduce sexual transmission of chlamydial STD and unwanded pregnancy:

1. Abstinence and reduction of number of sex partners

The most reliable way to avoid transmission of chlamydial STDs is to abstain from sex i.e., oral, vaginal or anal sex. Counseling that encourages abstinence from sexual intercourse is crucial for persons who are being treated for an STD or whose partners are undergoing treatment and for persons who want to avoid the possible consequences of sex completely e.g. unintended pregnancy. Screening before initiating sex might reduce the risk for future transmission of asymptomatic chlamydial infection.

2. Condoms

When used consistently and correctly, Latex male condoms are highly effective in preventing the sexual transmission of chlamydial infection and can reduce the risk for chlamydia.

Partner Management :

Partner notification ("contact tracing") :

Health care providers or public health authorities learn from persons with STDs about their sex partners and help to arrange for the evaluation and treatment of sex partners either directly or with assistance from state and local health departments by partner services. Many persons individually benefit from partner notification. When partners are treated, index patients have reduced the risk for re-infection. Partner notification can disrupt networks of chlamydia transmission and reduce disease incidence. Therefore, providers should encourage their patients with chlamydia to notify their sex partners and urge them to seek medical evaluation and treatment.

Reporting and Confidentiality :

The accurate and timely reporting is integrally important for assessing morbidity trends and assisting local health authorities in partner notification and treatment. Reports should be kept strictly confidential. (CDC MMWR 2006).

References:

1. Santos, C, Teixeira, F, vicente, A & Astofil-Fiho, S 2003,Detection of Chlamydia trachomatis in endocervical smears of sexually active women in Manaus-AM, Brazil, by PCR, BJID, vol.-7,no.2,pp.91-95.

2. Levinson, W 2009, Review of Medical Microbiology and Immunology, 10th edn, McGraw-Hill, pp 179.

3. Microbewiki 2011

4. Fredlund, H, Falk, L, Jurstrand, M, Unemo, M 2004, Molecular genetic methods for diagnosis and cherecterigation of chlamydia trachomatis and Neisseria gonorrhoea: impact on epidemiological,surveillance and interventions, APMIS,vol.112, pp771-84.

5. Lanjouw, E, Ossewaarde, J M, Stary,A 2010, European guideline for the manegment of chlamydia trachomatis infection,

6. CDC 2010, 'Chlamydia,' viewed 15 September 2010 <www.cdc.gov/std/chlamydia/stdfact-chlamydia.htm>.

7. Smith, JS, Munoz, N , Herrero, R, Eluf-Neto, J, Ngelangel, C , Bosch, FX, Walboomers, JMM & Peeling, RW 2002, 'Evidence for as a human papilloma virus cofactor in the etiology of Invasive

8. Clark,TJ n.d, Chlamydia trachomatis, viewed 14 November 2010, <http://www.tjclarkinc.com /bacterial_diseases/chlamydia_trachomatis.htm>

9. Schachter, J & Alexander, ER 1998, ' Chlamydial infections',in Bacterial infections of humans: epidemiology and control, eds Evans AS & Brachman PS, Spriger, Plenum publishing corporation, New York,pp.197-221, viewed 14 November 2010.

10. World Health Organization 2001, 'Global prevalence & incidence of selected curable sexually transmitted infections overview and estimates,' WHO, Geneva, viewed 12 April 2010, <httpp://www.who.int/docstore/hiv/GRSTI/index/htm >.

11. Wikimedia project 2010, Wikipedia, viewed 13 April 2010, <http://www.en.wikipedia.org / wiki/ Chlamydia Infection /biovar>.

12. Hammerschlag , MR 1981, ' Chlamydial Infections', Pediatrics in Review, vol.3,no.10, pp.77-84.

13. Dimitrakov, J 2002, "Chlamydia- A Journey from Embryonated Egg to LCR," The Prostatitis Foundation, viewed 9 september 2011, <http://www.prostatitis.org/chlamydia.html>

14. Eley, Adrian 2003, Chlamydia trachomatis is bad for your sperm, Microbiology Today, vol. 30, pp. 61-62.

15. Sexually Transmitted Diseases: Chlamydia - CDC Factsheet. http://www.cdc.gov/ std/chlamydia /stdfact-chlamydia.htm

16. Young, H, Moyes, A, Lough, H, Smith, IW, Mckenna, JG & Thompson, C 1991, Preliminary evaluation of "Clearview Chlamydia" for the rapid detection of Chlamydial antigen in cervical secretions,Genitourin Med, vol.67, pp. 120-123.

17. Pramanik, JM, Donde, UM, Maitra, A 2001, Use of polymerase chain reaction(PCR) for detection of infection in cervical swab sample, IJDVL, vol-67, no-5, pp2

18. Gao X, Chen X H, Yin Y P, Zhong Y M, Shi ,M,Q, Wei, W,H, Chen,Q, Peeling,R,W, Mabey,D 2007 Polymorphism Genotyping PCR-Restriction Fragment Length Women in China Performed Using trachomatis Serovars among High-Risk, J. Clin. Microbiol. vol 45(4), pp. 1185.

19. Mahony, JB, Luinstra, K,E, Sellors,J,W and Chernesky, MA 1993,Comparison of Plasmid- and Chromosome Based Polymerase Chain Reaction Assays for Detecting Chlamydia trachomatis Nucleic, J Clin Microbiol , vol.31, no.7, pp.1753-1758.

20. Shain, RN, Piper, JM, Holden, AE, Champion, JD, Perdue,ST & Korte, JE, 2004, 'Prevention of gonorrhea and Chlamydia through behavioral intervention: results of a two-year controlled randomized trial in minority women,' Sex Transm Dis, vol.31, pp.401-408.

21. Shrier,LA, Ancheta, R, Goodman,E, Chiou,VM, Lyden, MR & Emans,SJ 2001, 'Randomized controlled trial of a safer sex intervention for high-risk adolescent girls,' Arch Pediatr Adolesc Med, vol.155, pp.73-79.

22. Centers for Disease Control & Prevention 2006, Sexually transmitted diseases treatment guidelines , MMWR Recomm Rep, vol.51, no.RR-6, pp.1-78.