

Review Article

A must know compendium of genital chlamydia for health care providers

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Received: 01 March 2024

Revised: 09 April 2024

Accepted: 12 April 2024

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ABSTRACT

Chlamydia comprises the largest proportion of all sexually transmitted infections (STIs) worldwide. It is caused by *Chlamydia trachomatis*, an obligate intracellular bacterium and exists in two stages; an extracellular elementary body which is an infectious state and an intracellular reticulate body, a dormant state. The elementary body increases the risk of transfer of chlamydial infection during oral, genital or anal sex. On the other hand, the vegetative state of the reticulate body promotes the chance of latent and recurrent infection. In 2020, WHO estimated 129 million new chlamydia infections. Most of the chlamydial infections are asymptomatic (85-90%) which promotes transfer between partners. If untreated, it can lead to an ascending infection which greatly impacts sexual and reproductive health. In addition, it can infect the baby around childbirth and may result in stillbirth or neonatal death. The immuno-pathogenesis of the chlamydial infection is predominantly evoked by major outer membrane protein (MOMP), a dominant chlamydial antigen on the cell wall; along with the chlamydial antigen, heat shock protein 60 (HSP60) triggers host immune responses. The innate and adaptive immune responses result in extensive fibrosis and permanent damage to the fallopian tube resulting in tubal factor infertility and ectopic tubal pregnancy. The improved strategies in screening, diagnosis, treatment and follow up of Chlamydial infection can have noticeable effects on prevention of incidence, retarding the progression and avoiding recurrence of infection leading to a reduction in the global burden of STIs and the consequent adverse neonatal outcome.

Keywords: Genital chlamydia, ectopic pregnancy, pelvic inflammatory disease, NAAT

INTRODUCTION

Sexually transmitted infections (STI) have significant short- and long-term implications on the reproductive health of women. It causes adverse health effects with impact on their physical, emotional, financial and psychosocial wellbeing. Genital chlamydia trachomatis (CT) infections are the most common bacterial STI worldwide. The global estimate of new cases of CT infections reported by WHO in 2020 is 129 million cases.¹ In 2016, the estimated global prevalence of CT infections

in women and men aged 15-49 years was reported to be 3.8% and 2.7% respectively.² The greatest challenge faced in the natural history of progression and transmission of CT infection is that 85-90% of women and men are asymptomatic and thus remain undetected resulting in substantial reproductive morbidity.³ In women, it is a major cause of complications like pelvic inflammatory disease (PID), ectopic pregnancy (EP) and tubal factor infertility (TFI), in men, epididymitis and orchitis and in neonate conjunctivitis and pneumonia.⁴ The asymptomatic infection recommends the need for routine screening of CT

from urogenital specimens for early diagnosis and treatment of CT infections to prevent reproductive sequelae. Opportunistic CT screening is offered to young sexually active adults <25 years and those at high-risk (eg, new sex partner or multiple sex partners) attending healthcare services as per the STI guidelines.⁵

The lifecycle of chlamydia trachomatis

CT exists in biphasic stage: extracellular elementary body (infectious) and intracellular reticulate body (vegetative and noninfectious). Infection starts when elementary body adheres and invades the columnar epithelium of the urogenital tract. In 2 hours elementary body (EB) will be transformed to reticulate body (RB) inside the cell. After an incubation period of 7-21 days, RB divides every 2-3 hours by binary fission for 18-72 hours and form intracytoplasmic inclusion called ‘Halberstädter-Prowazek bodies’ (Scientists who discovered Chlamydia). RB will reorganize to infectious EB form and EB will be released by the cell (Figure 1). The host inflammatory response of production of gamma interferon (IFN- γ) can cause intracellular inclusions to stop replicating and be viable in persistent phase (cryptic form). This developmental arrest can be reactivated if IFN- γ release stops and RB can redifferentiate to EB causing propagation of the cycle. This cryptic form explains the chronic infection which can persist from months to years.⁶ The incubation period is between 7-21 days.⁷

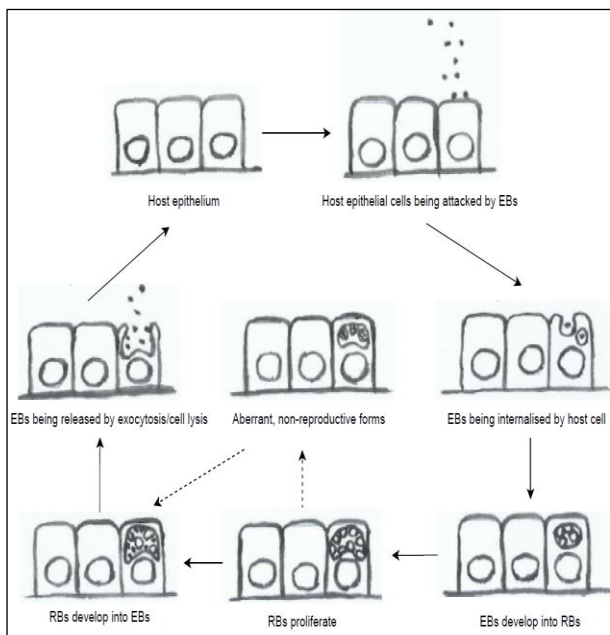


Figure 1: Developmental cycle of Chlamydia.

GENITAL CHLAMYDIA TRACHOMATIS INFECTION

Etiopathogenesis

Genital CT infection is caused by *Chlamydia trachomatis* serovars D-K, which is a gram negative obligate

intracellular bacterial pathogen and infects the mucosa of the lower urogenital tract, rectum, pharynx, conjunctiva and placenta. It is transmitted by oral, vaginal or anal sex, and can also be transmitted from mother to neonate during vaginal delivery. The risk of transmission from one episode of sexual intercourse is between 10 to 20%.⁸ Several studies have estimated the duration of asymptomatic infection to be between 1-18 months.⁸ If untreated, the infection can persist or clear spontaneously. Studies have shown that up to 50% of infections resolve spontaneously within 12 months of initial diagnosis because of adaptive and innate immune responses in host and biological properties of organism.⁹ However, the infection can ascend to the upper genital tract and cause symptomatic PID in 10-20% of women.⁶

Immunopathogenesis

CT infection triggers the release of proinflammatory cytokine (IL-1 α , IL-1 β , IL-6, IL-8, IL-10, IL-12, TNF α , IFN γ) which induce inflammatory response and recruitment of immune cells (dendritic cell, neutrophils, macrophages, lymphocytes, natural killer cells, B cells and T cells) responsible for innate and adaptive immune response. CD4+ mediated Th1 response and CD8+ play a crucial role in resolving the infection by production of IFN γ (Figure 2). Low levels of IFN γ can result in cryptic form which can cause persistence of infection for years and reactivation later. The host immune response does not provide long term immunity and recurrent infection can cause strong secondary immune response with further damage by fibrosis and scarring of the reproductive tract.¹⁰

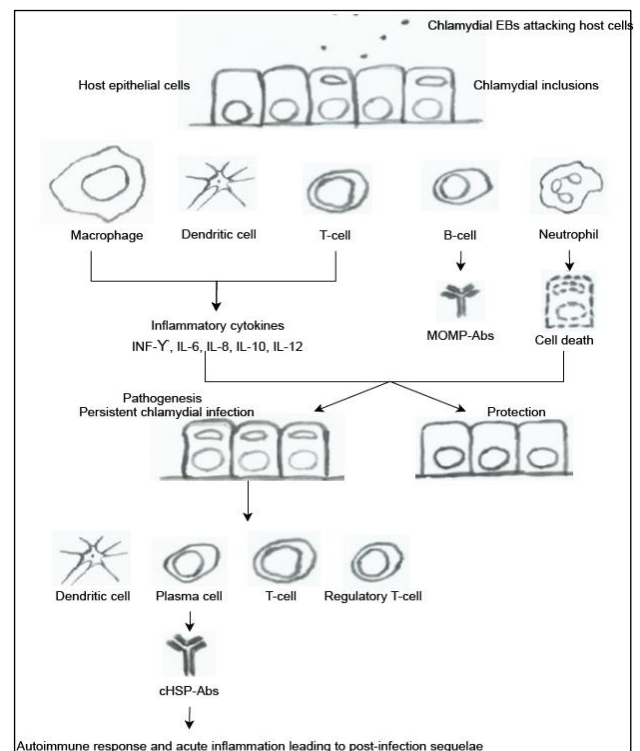


Figure 2: Mucosal immune response in chlamydial infection.

The pathogenesis depends on route of infection, infectious load on exposure, survival within the cell, innate and adaptive immune response, cytokine profile, HLA subtype, host genetic factors, chlamydial antigen and virulence of strain.

Chlamydial antigens such as major outer membrane protein (MOMP), chlamydial 60-kDa heat shock protein (cHSP60) and cHSP10 trigger the host immune responses and contribute to both protective immunity and pathogenesis.¹¹

Clinical presentation

Though mostly asymptomatic, one third of women can present with symptoms of mucopurulent vaginal discharge, dysuria, postcoital or irregular uterine bleeding, dyspareunia and abdominal or pelvic discomfort and local signs of infection on examination. Pelvic examination can reveal mucopurulent discharge from cervix, cervical ectopy and adnexal/cervical motion tenderness.³ The clinical manifestations of CT infections are shown in the Table 1.

Table 1: Clinical manifestations.

Women	Men
Acute urethral syndrome	Urethritis
Urethritis	Epididymo-orchitis
Bartholinitis	Proctitis
Cervicitis	Conjunctivitis
Endometritis	Reiter’s syndrome (urethritis, conjunctivitis, arthritis and mucocutaneous lesions)
Salpingo-oophoritis	Reactive tenosynovitis
Pelvic inflammatory disease	Sexually acquired reactive arthritis (SARA)
Tubo-ovarian abscess	
Ectopic pregnancy	
Tubal factor infertility	
Chronic pelvic pain	
Perihepatitis (Fitz-Hugh-Curtis syndrome)	
Reiter’s syndrome (urethritis, conjunctivitis, arthritis and mucocutaneous lesions)	
Sexually acquired reactive arthritis (SARA)<1%	
Proctitis	
Conjunctivitis	
Pharyngitis	
Cervical lymphadenopathy	
Pregnancy	
Preterm labour	
Premature rupture of membranes	
Low birth weight	
Neonatal death	
Postpartum endometritis	
Ophthalmia neonatorum	
Atypical pneumonia	

Diagnostic methods

CT infections can be diagnosed by direct and indirect methods. The direct methods are detection of pathogen by cell culture, antigen tests (enzyme immunoassay (EIA), direct fluorescent antibody (DFA), and rapid diagnostic test (RDT)), nucleic acid amplification test (NAAT) and nucleic acid hybridization or nucleic acid probe test. Indirect methods are serological tests to detect antibodies against CT. These tests are laboratory based or point of care test. Lab-based tests include NAAT, nucleic acid hybridization and transformation test, EIA, DFA and cell culture. Point of care tests include solid phase EIA or solid phase optical immunoassay.¹² Antigen tests are not recommended due to their low sensitivity and specificity (Figure 3).

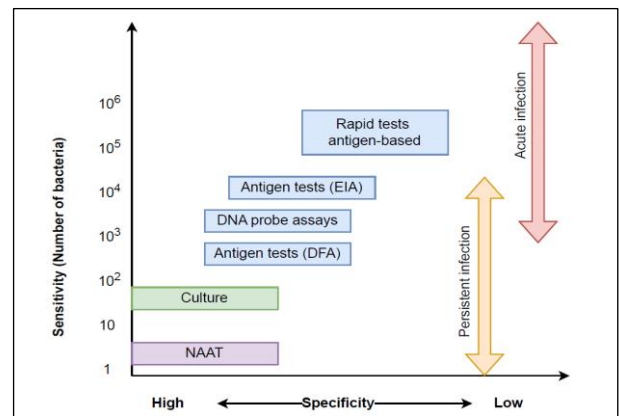


Figure 3: Sensitivity and specificity of lab tests in chlamydial infection.

CELL CULTURE OF CT

The clinical specimens for cell culture are swabs from anatomical sites (vagina, endocervix, urethra, anal canal, pharynx or conjunctivae) collected and transported in special media. The centrifuged specimen is monolayered on Mc Coy, HeLa 229 or Buffalo Green Monkey Kidney cells and analyzed for intracytoplasmic inclusions after 48-72 hours by staining with Giemsa, iodine or fluorescence labelled antibodies to chlamydial antigens (MOMP).

The detection rate of CT infection by cell culture is highly specific at 60-80% and it depends on viable organisms. However, sensitivity can be affected by inadequate specimen collection, storage, transport, chemicals and contamination by commensals. Furthermore, cell culture is labor intensive, time consuming and difficult to standardize. So, this diagnostic test is rarely done and is still used to monitor antibiotic susceptibility and virulent strains.¹³

NAAT

The gold standard test for screening and diagnosis of CT infections is NAAT because of their high sensitivity (>90%) and specificity (>99%) compared to other tests.¹⁴ NAATs are designed to amplify the nucleic acid sequences specific for CT. The advantage of NAAT over cell culture is that it does not depend on viable organisms and has high sensitivity because of their ability to detect even a single copy of target DNA or RNA. NAAT is mostly based on polymerase chain reaction (PCR) with automated nucleic acid extraction and uses fluorescence labelled probes to

detect amplification products in real time. The commercial NAAT differs in their amplification methods and their target nucleic acid sequences which are shown in table. The test result can be generated in a few hours.¹³

In order to reduce the time between testing and reporting, point of care test (POCT) using molecular and immunoassay, rapid NAAT has been developed with sensitivity (82-84%) and provides result in about 30 minutes. The Velox POC-test chlamydia (Atlas genetics) is based on electrochemical detection of PCR products in fluidic card.¹⁵

Single positive NAAT result has high positive predictive value in high prevalence population. However, a repeat test with a second platform is recommended in medicolegal cases. The disadvantage of NAAT is the presence of amplification inhibitors in biological specimens which can cause false negative test results. This is overcome by the modern nucleic acid extraction techniques which effectively removes most inhibitors.

On the contrary, false positive results are possible due to contamination which can be avoided by strict quality control measures. In 2006, nvCT, a new variant CT, a Swedish strain with 377 bp deletion in the cryptic plasmid was identified. This is due to genetic recombination and can result in new variants with increased virulence. The following table shows the different characteristics of the commercial automated NAAT platforms commonly available for the detection of CT in clinical specimens.⁹ Table 2 shows the comparison of NAAT tests in chlamydial infection.

Table 2: Comparison of NAAT tests in chlamydial infection.

Name of test	Abbott	BD	GenProbe	Roche
	Real-time CT/NG	BD probe tec	Aptima combo AC2	Cobas c4800
Amplification method	Real-time PCR	Strand displacement amplification (SDA)	Transcription mediated amplification (TMA)	Real-time PCR
Chlamydia trachomatis targets	Cryptic plasmid (dual targets)	Cryptic plasmid	23S rRNA	Cryptic plasmid and ompA gene (dual targets)
nvCT detection	Yes	Yes	Yes	Yes
Plasmid free Chlamydia trachomatis detection	No	No	Yes	Yes
Confirmation test using an alternative target	No	No	Yes (16S rRNA)	No
Internal control	Internal control (from extraction to amplification)	extraction control only, no amplification control	None	Internal control (from extraction to amplification)
Validation for extra-genital site testing	No data	Rectal (sensitivity 63%); oropharyngeal (sensitivity 67%)	Rectal (sensitivity 93%); oropharyngeal (sensitivity 100%)	sensitivity for rectal CT: 91.4% to 95.8% old version

NAAT is done at the time of initial presentation and a repeat test is recommended if there is concern of sexual exposure within 2 weeks. The window period is usually 2 weeks. So, repeat NAAT is advised 2 weeks after sexual exposure.

NUCLEIC ACID HYBRIDIZATION (PROBE) TEST

GenProbe PACE2 and Digene hybrid capture assays are nucleic acid probe tests approved by FDA. In GenProbe hybridization assay, a DNA probe that is complementary to a specific sequence of CT rRNA hybridizes with complementary rRNA present in specimen. In Digene assay, RNA hybridization probes are specific for both genomic and cryptic plasmid DNA sequence of CT. The advantage of this test is ability to store and transport specimen for up to 7 days without refrigeration before testing.¹²

EIA

EIA test detects chlamydial LPS with a monoclonal or polyclonal antibody that is labelled with an enzyme. The enzyme turns the colorless substrate into colored product which can be detected by a spectrophotometer. The advantage of the test is that it can be stored and transported without refrigeration within the time instructed by the manufacturer. The disadvantage is the possibility of false positive test results due to cross reaction with LPS from other microorganisms including other chlamydial species.¹²

DFA TEST

The chlamydial antigen (MOMP/LPS) is detected by DFA test by rolling the specimen in the well of the slide. After the slide dries, fixative is added, and the slide transported to the lab to be processed within 7 days. In the lab, fluorescein-labelled monoclonal antibody binds to CT elementary bodies which appears stained by fluorescence microscopy. Monoclonal anti-MOMP is specific for CT. However, anti-LPS monoclonal antibody can cross react with other chlamydial species and microorganisms. DFA test requires the lab technician to be well trained in fluorescein microscopy to identify fluorescein coated CT elementary bodies and the procedure is tiring and time consuming.¹²

SEROLOGICAL TESTS

Serological tests is of limited use because of antibody cross reactivity with other species. It is not useful in acute infections. However, positive serology may be helpful in the diagnosis of chronic infections like PID, SARA etc. The micro immunofluorescence (MIF) test for chlamydia antibody testing is subjective, labour intensive and time consuming. Currently, EIA and immunoblots or line assays are used to detect chlamydia antibodies. The serological test can be improved by using species-specific proteins or peptides. The proteome-array is used to compare antibody

profile in tubal factor infertility (TFI) and normal fertility. Recent studies have identified different antibody reactivity in acute and chronic CT infection which might be used to categorize antibody panels as possible markers for different stages of infection.¹³

SAMPLING SITES

In women, vulvovaginal swab (self-taken or taken by health care worker) is the specimen of choice and is collected by inserting the swab about 2-3 inches into the vagina and gently rotating for 10-30 sec. Vulvovaginal swab has sensitivity of 96-98% and is better with patient acceptance and adequacy of specimen than endocervical and urine specimens.⁹

In men, first catch urine (FCU) is the sample of choice, more acceptable and has the highest organism load than the urethral swab. FCU collects the first 20 ml of urine after holding the urine for 1 hour.

Table 3: Sampling sites in chlamydial infection.

Women	Vulvovaginal, endocervical, first catch urine (FCU), rectal, oropharyngeal
Men	FCU, urethral, rectal, oropharyngeal

MANAGEMENT

General advice

Individuals with CT infection should be advised sexual abstinence for seven days after completion of treatment or until the symptoms completely resolve. They must be provided with written or web-based detailed information regarding natural history of transmission of CT, clinical symptoms, complications, treatment and prevention of recurrent infection. In addition, testing for other STIs (HIV, hepatitis B, syphilis, gonorrhoea) should be considered. If the individual is suspected to be in window period, the screening tests must be repeated after appropriate time interval. All sexual contact within 6 months period must be contacted, screened and treated to prevent spread of infection and recurrence. Also, advise on safe sexual practices including correct and consistent condom usage.¹⁶

Indications for treatment

The indications for treatment are as follows- (a) screening or diagnostic test positive for NAAT for CT for patient or partner; (b) CT confirmed in neonate; (c) sexual assault; and (d) clinical symptoms of CT.

Clinical samples must be taken for lab assessment before starting treatment when CT is suspected. If POC test is available, it helps in immediate treatment of positive patient because of their advantage of quick results.

Treatment

The current first line treatment recommendation for uncomplicated urogenital, pharyngeal or rectal CT infections is oral doxycycline 100mg twice a day for 7 days. If a patient is allergic or intolerant to doxycycline or pregnant, a single dose of azithromycin 1g orally followed by 500mg daily for 2 days is advised. This current extended course of azithromycin will also cover *Mycoplasma genitalium* (MG) if present because studies have reported coinfection rates of 3-15% with CT. Single dose azithromycin (SDA) has been widely used for STIs which resulted in macrolide resistance, treatment failure up to 8% in recent studies and ineffective treatment of rectal CT and MG.¹⁷

Both doxycycline and single dose azithromycin are highly effective in the treatment of urogenital CT infections with cure rate of 98% and 97% respectively. However, recent meta-analysis has shown a small 3% but statistically significant benefit of doxycycline over azithromycin in urogenital CT infections and 7% increase in benefit in men with symptomatic urethral CT infection.¹⁸ Another study has reported 19.9% difference in efficacy in favor of doxycycline for rectal CT infection.¹⁹

Alternative regimen (if first line treatment is contraindicated)

The regimen was (a) oral erythromycin 500 mg twice daily for 10-14 days; (b) oral ofloxacin 200 mg twice daily or 400 mg once daily for 7 days (contraindicated in pregnancy); (c) oral levofloxacin 500 mg once daily for 7 days (contraindicated in pregnancy); and (d) oral Josamycin 500 mg thrice daily or 1000 mg twice daily for 7 days (as third line).

HIV positive

HIV positive patients should be treated the same way as non-HIV individuals.

Pregnancy and breast feeding

The regimen was (a) oral azithromycin 1 g single dose followed by 500 mg daily for 2 days; (b) oral erythromycin 500 mg four times daily for 7 days; (c) oral erythromycin 500 mg twice daily for 14 days; (d) oral amoxicillin 500 mg thrice daily for 7 days; and (e) azithromycin is better tolerated than erythromycin during pregnancy. A study has shown that 19% of pregnant women discontinued erythromycin due to its side effect compared to 2% with azithromycin.

TEST OF CURE (TOC)

TOC is not recommended for uncomplicated CT infections because residual, non-viable CT DNA may be detected by NAAT for 3-5 weeks after completion of treatment.

Indications for TOC include rectal CT infection, during pregnancy, breast feeding, on alternative regimen, suspected poor compliance and if symptoms persist. There are inadequate studies on optimal time for TOC performance. However, TOC should not be advised before 3 weeks of completion of treatment.

Positive tests after treatment can be due to poor compliance, reinfection from untreated or new partner, inadequate treatment or false positive result.

REINFECTION AND REPEAT TESTING

Reinfection is common with CT infection and usually occurs within 2-5 months of previous infection. It is very difficult to differentiate between treatment failure and reinfection. TOC is different from testing for reinfection. In view of the complications associated with recurrent infections, many countries recommend repeated testing at intervals of 3-12 months in infected high-risk individuals as a part of the chlamydial screening program.

Contact notification, tracing of sexual contacts and follow up is of paramount importance in the prevention of reinfection and in decreasing the prevalence of CT. If contact does not attend for screening, expedited partner therapy or patient delivered partner therapy can be effective in preventing reinfection.¹⁶

Follow-up

Follow-up by attendance at clinic or telephone is recommended because it provides an opportunity to enhance treatment compliance, encourage sexual abstinence until treatment is completed and also reinforce health education.⁹

DISCUSSION

Chlamydial infections of the genital tract are preventable, treatable, and curable STIs which affect adults of all age groups worldwide. In 2020, the global prevalence of chlamydial infections among individuals between 15-49 years was estimated to be 4% for women and 2.5% for men.²⁰ Most chlamydial infections are asymptomatic and hence promote transmission and acquisition of infection sexually. The mucosal adherence of the organism to the columnar epithelium of the endocervix incites an inflammatory and immune response and contributes to the development of innate and adaptive immunity.¹⁰ If left untreated, infection can have adverse effects on the genitourinary tract of men and women. In pregnant women, chlamydial infection can cause serious consequences in the unborn fetus and neonate increasing the perinatal morbidity and mortality. In addition, puerperal infection can result in endometritis and increase maternal morbidity.³

The mainstay of investigation to diagnose chlamydial infection is NAAT. A wide array of NAAT-RDTs is

available which have high sensitivity and specificity to detect chlamydial infection.¹³ These tests are recommended 2 weeks after suspected exposure and repeated if necessary.

A repeat test is not routinely recommended and is advised 3 weeks after completion of treatment in indicated cases. The countries which have National chlamydial screening program advocate vulvovaginal swab in women and first catch urine samples in men to detect chlamydial infection. Studies have underscored the importance of screening programs by demonstrating early detection of chlamydial infections and appropriate treatment in regions where screening programs are in place for individuals with risk factors.³ The treatment of choice for uncomplicated chlamydial infection is oral doxycycline 100mg twice daily for 7 days.¹⁷

In pregnant women, oral azithromycin is the drug of choice as doxycycline is not recommended during pregnancy. Health education about sexual hygiene and implications of STIs and regular follow-up can promote sexual and reproductive wellbeing of people and decrease the recurrence risk.²¹ The United Nations Sustainable development goal 3 (SDG-3) focuses on good health and wellbeing for all at all ages. Knowledge, awareness and appropriate attitude of individuals at risk of STIs can assist in overcoming this serious public health concern and achieving SDG-3.

CONCLUSION

Chlamydia trachomatis is the most common curable bacterial sexually transmitted infection with adverse reproductive consequences in young adults. This rationalizes the need for chlamydial screening program in many countries to detect and prevent the adverse outcomes. Due to the host genetic and immune factors, replication in infected cells varies considerably and is very low in asymptomatic and persistent infections. NAAT is the gold standard test in detection of CT. Recently, novel methods of rapid NAAT diagnostic tests are available which effectively decreased the reporting time to less than 30 minutes facilitating immediate start of treatment and reducing the waiting period and complications. Doxycycline and extended course of azithromycin are the recommended first line treatment for urogenital, pharyngeal and rectal CT infection. It is important to ensure patient compliance, sexual abstinence, patient education and partner or contact notification, evaluation, screening and treatment for optimal treatment outcome. TOC is advised if compliance is in question, symptoms persist, in pregnancy and rectal CT infection. Expedited partner therapy or patient -delivered partner therapy may be an option if partner does not wish to be evaluated or access to health care is not available. The CT transmission can be prevented by effective implementation of the screening program, prompt treatment of asymptomatic infection, patient counselling, health education, safe sexual practice and follow-up.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Ponnupillai A, Madhavan P, Patil SS, Earnest BSP. A must know compendium of genital chlamydia for health care providers. *Int J Community Med Public Health* 2024;11:2071-8.