

Management of Sexually Transmitted Diseases

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Abstract

Sexually transmitted diseases (STD) are a variety of infections which are caused by the microorganisms including viruses that are acquired through sexual contact. These infections are manifested as various group of symptoms or syndromes. Early diagnosis and complete treatment remains the keystone for reducing the burden and preventing transmission. Health care providers must be well versed with the strategy of treatment and prevention of these STDs. Complete treatment of some of these infections take months and hence close patient and contact follow up is required.

Introduction

The global health burden of sexually transmitted diseases and Human Immunodeficiency Virus (HIV) infections is large and increasing. Sexually transmitted infections are caused by diverse group of microorganisms. Many individuals have asymptomatic early infections which favor onward transmission and delay in diagnosis. Apart from the serious complications of sexually transmitted infections, the greatest threat is posed by the fact that they favor acquisition and transmission of HIV [1,2,3]. Therefore a coordinated multiagency approach involving health, education and other government departments is required with emphasis on behavior change and condom use during sex. This review discusses the diagnosis and treatment protocols of the major sexually transmitted infections – anogenital warts, genital ulcer diseases (herpes genitalis, chancroid, syphilis), granuloma inguinale,

lymphogranuloma venereum, gonorrhoea and genital chlamydia infections.

Anogenital Warts

Anogenital warts are caused by Human Papilloma Virus (HPV), more than 90% cases by HPV 6 and 11.

Treatment

I. For external anogenital warts [1,4,5]

Patient applied	Provider administered
Imiquimod 3.75% or 5% cream	Cryotherapy with liquid nitrogen
Or Podofilox 0.5 % solution/ gel	Or Surgical removal by scissor/ shave excision, curettage, laser or electro surgery
Or Sinecatechins 15% ointment	Or Trichloroacetic acid (TCA)/ Bichloroacetic acid (BCA) 80-90% solution
	Or Podophyllin resin 10-25% in compound tincture of benzoin
	Or Intra-lesional interferons

II. For urethral meatus warts [1, 5] : Cryotherapy with liquid nitrogen
Or surgical removal

III. For vaginal / cervical/ intra-anal warts [1, 5] : Cryotherapy with liquid nitrogen
Or Surgical removal
Or TCA/ BCA 80-90% solution

Table showing treatment options for anogenital warts, regime, instructions and their adverse effects [1, 4]

	Regime	Special instructions	Adverse effects
Imiquimod 5% / 3.5% cream	5% cream : once at night time for 3 days per week for maximum upto 16 weeks 3.5% cream: once daily at night time	Wash with soap and water 6-10 hrs after application	Local irritation, redness, induration, vesiculation, hypopigmentation. Limited data in pregnancy

Podofilox (podophyllotoxin) 0.5% solution or gel	Twice daily for 3 consecutive days of week for maximum up to 4 weeks	Total area should not exceed 10 sq. cm Total volume should not exceed 0.5 ml/day	Local irritation with mild to moderate pain Contraindicated in pregnancy
Sinecatechins (green tea extract) 15% ointment	Thrice daily (0.5 cm strand of ointment is applied to each wart) for maximum up to 16 weeks	Do not wash Avoid sexual contact while ointment is on skin	Local inflammation Not given in HIV, pregnancy, genital herpes
Cryotherapy	Once per week	Local anesthesia might facilitate if area is large	Pain during and after application, necrosis, blistering
TCA, BCA 80-90% solution	Once per week	Use small amounts Allow to dry before patient sits/stands If applied in excess or in case of pain, neutralize with soda bicarbonate, liquid soap or talc	Spreads to adjacent tissues
Podophyllin 10-25% in compound tincture of benzoin	Once per week	Wash after 1-4 hrs Use <0.5 ml per session and on <10 sq. cm area of warts Treatment area should not have open wounds/ friable tissue	Local inflammation Due to systemic toxicity, no longer recommended Not safe in pregnancy

Chancroid

Chancroid is a genital ulcer disease caused by bacterium *Haemophilus ducreyi*.

Diagnosis: All persons with genital/ anal/ perianal ulcers should be evaluated and following investigations should be done [6,7,8] :

1. Test for *Haemophilus ducreyi* - Direct smear is recommended as the first step, although it

lacks both sensitivity and specificity for definite diagnosis. Smear is taken from the base of the ulcer and stained with Gram's or Giemsa stain. The bacilli are seen as gram negative coccobacilli, with a typical 'school of fish', 'rail-road track' or 'finger prints' appearance. A definite diagnosis require growing of organism in culture which include gonococcal agar base

with 2% bovine hemoglobin and 5% fetal calf serum and Mueller-Hinton agar with 5% cholelized horse blood.

2. Syphilis serology / dark field examination/ Polymerase Chain Reaction (PCR) for treponema pallidum deoxyribo-nucleic acid (DNA)

3. Culture / PCR for genital herpes

For clinical purposes, diagnosis of chancroid is made if all of the following criteria are met [1,7] :

1. One or more painful genital ulcers
2. Painful genital ulcer with regional lymphadenopathy (typical for chancroid)
3. No evidence of treponema pallidum by dark field examination of ulcer exudates or by serologic test for syphilis performed at least 7 days after onset of ulcer
4. Negative Herpes Simplex Virus (HSV) culture / PCR

Treatment

The sexually transmitted diseases guidelines, 2015 by Centers for Disease Control and Prevention (CDC) [1,5] recommends the following regimens:

Azithromycin 1g orally single dose

Or Ceftriaxone 250 mg intramuscular injection single dose

Or Ciprofloxacin 500 mg twice a day orally for 3 days

Or Erythromycin 500 mg thrice a day orally for 7 days

Incision and drainage of bubo is preferred over needle aspiration. Sex partners should be treated if there is history of sexual contact during 10 days preceding onset of symptoms in patients.

In pregnancy, Ciprofloxacin is avoided but antimicrobials like Erythromycin and Ceftriaxone can be used for its treatment.

In HIV infected person same drugs are used, however, treatment for longer period may be required.

Genital Herpes

Genital herpes is mostly caused by Herpes Simplex Virus 2 (HSV2). However cases caused HSV1 have been reported recently.

Diagnosis: HSV infection can be diagnosed by the following investigations [1,6,8]:

1. Tzanck smear: Smear is taken from the base of a vesicle or erosion and stained with Giemsa stain which may show multinucleated giant cells. But this test is usually insensitive and may be negative in later lesions.
2. Viral culture from vesicle fluid: It is not done routinely as the viral cultures are not available in most laboratories.
3. Immunofluorescence can be done to demonstrate viral antigen but it lacks sensitivity.
4. PCR for HSV DNA is the most reliable test and also the investigation of choice for herpes encephalitis and aseptic meningitis.
5. Type specific serology is indicated in case of recurrent symptoms but with negative HSV PCR/ culture.

Treatment

The regimen recommended by CDC 2015 guidelines [1,9,10] for herpes genitalis is as follows:

A. First clinical episode

Acyclovir 400 mg orally thrice daily for 7-10 days

Or Acyclovir 200 mg 5 times a day for 7-10 days

Or Valacyclovir 1g twice daily orally for 7-10 days

Or Famcyclovir 250 mg thrice daily orally for 7-10 days

B. Episodic therapy for recurrent genital herpes

Acyclovir 400 mg thrice daily orally for 5 days

Or Acyclovir 800 mg twice daily orally for 5 days

Or Acyclovir 800 mg thrice daily for 2 days

Or Valacyclovir 500 mg twice daily orally for 3 days

Or Valacyclovir 1g once daily for 5 days

Or Famcyclovir 125 mg twice daily for 5 days

Or Famcyclovir 1g twice daily for 1 day

C. Suppressive therapy for recurrent genital herpes

Acyclovir 400 mg twice daily

Or Valacyclovir 1g once daily

Or Famcyclovir 250 mg twice daily

D. In severe disease/ disseminated disease/ Central nervous system(CNS) complications

Acyclovir 5-10 mg/kg intravenous 8 hourly for 2-7 days followed by oral antiviral to complete at least 10 days of total therapy (21 days of I/V therapy in HSV encephalitis).

E. In persons with HIV

	Episodic treatment	Suppressive therapy
Acyclovir	400 mg thrice daily orally for 5-10 days	400-800 mg 2-3 times daily
Or Valacyclovir	1g twice daily for 5-10 days	500 mg twice daily
Or Famcyclovir	500 mg twice daily for 5-10 days	500 mg twice daily

F. Suppressive therapy in pregnant women with recurrent genital herpes

Antivirals should be started at 36 weeks gestation for prevention of neonatal herpes

Acyclovir 400 mg thrice daily orally

Or Valacyclovir 500 mg twice daily orally

G. Neonatal Herpes [1,11,12]

1. **Scenario 1** : When mother develops primary genital herpes at the time of delivery



Maximum chances of transmission from mother to child (50%) → severe and fatal neonatal herpes



Caesarean section done and I/V Acyclovir to child is given

2. **Scenario 2** : When mother develops primary genital herpes in third trimester → Foetal growth retardation and premature birth



Treatment of mother with oral Acyclovir

3. **Scenario 3** : If mother has history of genital herpes but no active infection during pregnancy → monitor the baby and test for HSV.



Treatment of neonatal herpes: intravenous Acyclovir 60 mg / day in 3 divided doses for 2-3 weeks followed by oral Acyclovir for 6 months.

Syphilis

Syphilis is caused by spirochaetal bacterium *Treponema pallidum*.

Diagnosis: Following investigations can be done for diagnosis of syphilis [1,2,5,13,14,15]:

Presumptive diagnosis is made by:

NON TREPONEMAL TESTS	TREPONEMAL TESTS
<p>Titres correlated with disease activity and used to follow up treatment response. 4-fold change in titre is significant</p>	<p>Once positive remains positive throughout life</p>
<p>VDRL (Venereal disease research laboratory)</p> <p>RPR (Rapid plasma reagin)</p>	<p>FTA-Abs (Fluorescent treponemal antibody absorbed test)</p> <p>TPPA (Treponema pallidum passive particle agglutination assay)</p> <p>EIA (Enzyme immunoassay)</p> <p>TPHA (Treponema pallidum haemagglutination assay)</p>

Definite diagnosis is made by:

1. Dark field examination
2. PCR for treponemal DNA

Screening is performed by either EIA or combined VDRL/ TPHA. Positive results are confirmed by treponemal test of different type. It is essential to confirm presumptive serological diagnosis of syphilis on second specimen.

Diagnosis of neurosyphilis is made by a combination of abnormal cerebro spinal fluid (CSF) cell count/ protein, reactive CSF VDRL (highly specific but insensitive), reactive serologic test in the presence of neurological signs and symptoms.

Treatment [1,2,5,13,15]

A. First line

- 1) Early Syphilis (Primary, secondary, early latent)

Benzathine penicillin G 2.4 mega units intramuscular (I/M) injection single dose

Or Procaine penicillin G 0.6 mega units I/M once daily for 10 days

- 2) Late latent and cardiovascular syphilis

Benzathine penicillin G 2.4 mega units I/M weekly for 3 weeks (days 1, 8, 15)

Or Procaine penicillin G 0.6 mega units I/M daily for 17 days
- 3) Neurosyphilis

Procaine penicillin 2 g I/M daily + Probenecid 500 mg four times a day for 17 days

Or Benzyl penicillin 18-24 mega units daily, given as 3-4 mega units I/V every 4 hrs for 17 days

B. Second line

- 1) Early syphilis

Doxycycline 100 mg twice daily orally for 14 days

Or Erythromycin 500 mg four times a day for 14 days

Or Azithromycin 500 mg once daily for 10 days

Or Ceftriaxone 500 mg I/M inj. daily for 14 days (if no allergy to Penicillin)
- 2) Late latent and cardiovascular syphilis, neurosyphilis

Doxycycline 200 mg twice daily for 28 days (if allergic to Penicillin)
Or Amoxicillin 2 g thrice daily + Probenecid 500 mg QID for 28 days

First line in pregnancy: Procaine penicillin G

Follow up: Two years follow up is advised in latent or tertiary syphilis. Quantitative non treponemal test is repeated at 3 months, 6 months and each 6 months thereafter. Follow up for life is advised for cardio/ neurosyphilis.

Lymphogranuloma Venereum (LGV)

LGV is caused by one of the three serovars (L1, L2, L3) of *Chlamydia trachomatis*. It is clinically characterized by tender inguinal and /or femoral lymphadenopathy- usually unilateral, with or without genital ulcer/ papule. Proctocolitis is a primary manifestation in those engaged in anal intercourse. Outbreaks of proctocolitis have been reported in men having sex with men (MSM).

Diagnosis: Keeping in mind the clinical picture of patient and epidemiological information in the area, diagnosis is usually made by excluding all other differential diagnosis.

Genital lesions/ rectal specimens/ lymph node aspirate can be tested for *Chlamydia trachomatis* by culture/ direct immunofluorescence/ nucleic acid amplification test. PCR based genotyping can differentiate between LGV and Non- LGV *Chlamydia trachomatis* in rectal specimen. Complement fixation test more than or equal to 1:64 and microimmunofluorescence more than or equal to 1:256 support diagnosis [1,16,17].

Treatment [1,16,17]

Incision and drainage of bubo/ aspiration AND

Doxycycline 100 mg orally twice daily for 21 days
Or Erythromycin 500 mg four times a day for 21 days

Or Azithromycin 1g orally once a week for 21 days

Sex partners who have had contact within 60 days before onset of patient's symptoms should be examined and tested for urethral/ cervical/ rectal chlamydial infection. Presumptive treatment with Azithromycin 1 g orally single dose should be given.

Drug of choice in pregnancy is Erythromycin.

Granuloma Inguinale

It is genital ulcerative condition caused by *Klebsiella granulomatis* characterized by subcutaneous granulomas (pseudo-bubo) and absence of lymphadenopathy.

Diagnosis: Diagnosis is made by demonstration of dark staining 'Donovan bodies' on tissue crush preparation or biopsy. 'Donovan bodies' are found in large mononuclear cells of monocyte/ macrophage lineage, whose cytoplasm contains numerous organism 0.5-0.7 X 1-1.5 micrometer in size, that show bipolar staining (safety pin appearance). Successful culture of causative organism has been reported in human peripheral blood monocytes and Hep2 cells [1,18,19].

Treatment [1,18,19]

Azithromycin 1g orally once a week or 500 mg daily

Or Doxycycline 100mg twice daily

Or Ciprofloxacin 750 mg twice daily

Or Erythromycin 500 QID

Or Cotrimoxazole 960 mg twice daily

For at least 6 weeks and until all lesions completely heal

Add Gentamycin 1mg/kg I/V 8 hourly if no response is seen within first few days of treatment.

Treat sex partners who have had contact within 60 days before onset of symptoms in patients.

Erythromycin or Azithromycin can be given to treat granuloma inguinale in pregnancy and lactation

Investigations: [20, 21]

1. Presumptive diagnosis by demonstration of Gram negative intracellular diplococci within phagocytes in stained smears from anogenital sites. Sensitivity is 90-95 % in males with urethral discharge.
2. Culture is the gold standard for diagnosing gonorrhea which is 100 % specific.
3. Nucleic acid amplification test (NAAT) is more sensitive than culture.

Gonorrhoea

Gonorrhea is caused by *Neisseria gonorrhoeae*. It results in a number of clinical syndromes including urethritis, cervicitis, epididymo-orchitis, pelvic inflammatory disease, disseminated gonococcal infection and ophthalmia neonatorum.

Treatment [22,23]

First line	Ceftriaxone 500 mg intramuscular injection + Azithromycin 2g orally stat dose
Second line	Ceftriaxone 500 mg I/M injection Or Spectinomycin 2 g I/M inj + Azithromycin 2 g stat orally Or Cefixime 400 mg orally stat + Azithromycin 2g orally stat
Third line	Ciprofloxacin 500 mg orally + Azithromycin 2 g stat orally
Gonococcal epididymo-orchitis	Ceftriaxone 500mg I/M + Azithromycin 2 g orally stat followed by Doxycycline 100mg twice daily for 10-14 days
Pelvic inflammatory disease	Ceftriaxone 500mg I/M + Azithromycin 2 g orally stat followed by Doxycycline 100mg twice daily for 10-14 days + Metronidazole 400 mg twice daily for 10-14 days
Gonococcal conjunctivitis	Azithromycin 2 g orally stat + Ceftriaxone 500 mg I/M once daily for 3 days

Genital Chlamydia Infection

Genital Chlamydia infection is caused by *Chlamydia trachomatis* and is characterized by inflammation of genital and rectal mucous membrane; conjunctiva often asymptomatic.

Investigations: Nucleic acid amplification test is

now the only recommended diagnostic test for Chlamydia. Genotyping will differentiate between LGV and non LGV infections. A first void urine is the sample of choice in men and in females, a self-taken vaginal swab or endocervical swab is also acceptable [21].

Treatment [1, 5]

First line	Azithromycin 1 g orally stat (including in pregnancy)
Second line	Doxycycline 100 mg twice daily for 7 days
Third line	Ofloxacin 200-300 mg twice daily for 7 days Or Amoxicillin 500 mg QID for 7 days (in pregnancy only)
Chlamydial PID	Ceftriaxone 250 mg I/M injection single dose + Doxycycline 100 mg twice daily for 14 days + Metronidazole 400 mg twice daily for 14 days
Epididymo-orchitis	Ceftriaxone 500 mg I/M single dose + Doxycycline 100 mg twice daily for 14 days
Chlamydia associated with reactive arthritis	Rest and Non-Steroidal Anti Inflammatory Drugs (NSAID)

Conclusion

Effective prevention and treatment of sexually transmitted diseases can be achieved using a combination of responses constituting the 'public health package'. The essential components of this package are promotion of safe sex behavior, condom distribution program, promotion of health care seeking behavior, specific services to population at risk such as female and male sex workers, comprehensive case management of sexually transmitted infections and early detection

of symptomatic and asymptomatic infections. For comprehensive case management, it is essential that an early diagnosis is made through laboratory tests or syndromic approach. Patients should be informed the importance of taking full course of treatment. Counseling should be made available for cases where it is needed. Partner notification and treatment are essential elements of any STI control programme. These actions should be carried out with sensitivity, taking social and cultural factors into account, in order to avoid ethical problems.

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