STI MANAGEMENT GUIDELINES

7th Edition

DSC Clinic

OCTOBER 1, 2021

DEPARTMENT OF STI CONTROL (DSC)

PREFACE

This 7th edition of the DSC clinic STI Management Guidelines is designed to serve as a concise and comprehensive reference for doctors, nurses, allied health, and counsellors managing STIs in Singapore. We are also going green by not publishing physical copies & having this available as an online resource.

We have reviewed all the chapters and have updated them based on local antibiotic sensitivities, local experience and expertise, with reference to available international guidelines.

Currently, there is global and local concern with the rise in bacterial STIs like chlamydia, gonorrhoea & syphilis. Antibiotic resistance, especially of gonorrhoea, and availability of options for persons with a penicillin allergy may compromise timely and effective treatment.

In this edition, there are new chapters on HIV pre-exposure prophylaxis (PrEP), management of *Mycoplasma genitalium*, and STI screening of transgender individuals. There is also a new flowchart for HPV screening in females.

We hope you will find this guideline useful. We also welcome feedback and suggestions on ways to improve it.

Finally, as editor, I would like to thank the co-authors & contributors for their valuable contribution, and the staff at DSC clinic for their excellent work & continued support.

Editor
A/Prof Martin Chio

Co-authors & contributors
Prof Roy Chan
Dr Benson Yeo
Dr Ellen Chan
Dr Kuan Ling Yee
Dr Koh Yun Pei
Dr Tan Wei Sheng
Dr Coni Liu
The DSC Clinic team:
Theresa Soon, Mohd Adnan, Siti Aminah, James Foong, Germaine Chua, Izza Haziqah
Dr Gabriel Yan
Dr Tay Woo Chiao

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PRINCIPLES OF STI MANAGEMENT

1. HISTORY

To start taking the history, it is easier with questions related to the primary complaint. For male patients, presenting symptoms are urethral discharge, dysuria, anogenital ulcers, rashes or growths; whereas female symptoms include vaginal discharge, dysuria, anogenital ulcers, rashes or growths. Pharyngeal and rectal infections may be and are usually asymptomatic.

The sexual history of a patient with, or suspected to have, an STI/HIV should include:

- Recent sexual exposure: usually the last and second last partner, which include spouse, casual or regular partner, sex worker, regardless of gender, local or overseas status, and/or number of sexual partners throughout lifetime
- Type of sexual exposures: oral, vaginal, anal
- Use of condoms: for oral, vaginal, anal sex
- Use of lubricants / toys / other implements
- Use of non-barrier contraceptives
- Previous STIs and/or previous STI screening, if applicable

It is important to note that reliable history is only possible in a setting of privacy, confidentiality and if the healthcare provider has a non-judgemental attitude.

Other relevant medical information should include:

- Drug allergies
- Current medications which may interact with STI treatment
- Traditional medications
- Prior treatment
- Self-medication
- Menstrual, gynaecologic and obstetric history in females

After a reliable history is obtained, you will be able to ascertain the patient's risk of contracting an STI/HIV, order the relevant laboratory investigations and give advice to prevent acquisition in future.

2. PHYSICAL EXAMINATION

The anogenital and inguinal regions should be exposed and carefully examined in good lighting. Males can be examined lying on the examination couch (preferred) or standing up. Females should be examined in the lithotomy position. Proctoscopic examination should be performed on males and females who practice anal intercourse. If indicated, a general examination should be performed when there is the suspicion of syphilis, sexually acquired reaction arthritis (Reiter's), disseminated gonococcal infection and/or HIV infection.

3. LABORATORY INVESTIGATIONS

The correct use of laboratory tests in STI management include:

- Obtaining adequate specimens for direct smears, cultures and other detection methods e.g. molecular detection/PCRs.
- Ordering the appropriate blood tests, taking into consideration window periods.
- Proper storage and transport of the specimens.
- Accurate interpretation of the test results.

Tests of little or doubtful value, in the management of acute infections, should not be performed; these include serology tests for chlamydia, gonorrhoea and candida, and non-specific serological tests for herpes simplex virus. There are increasing examples of point-of-care rapid tests for HIV, syphilis, chlamydia and gonorrhoea. While convenient, they need to be used only when their performance has been adequately evaluated & approved by HSA. Rapid tests for HIV and syphilis are generally accurate. NAAT-based point-of-care tests for; those for chlamydia and gonorrhoea have shown promising results in clinical trials.

4. MAKING A DIAGNOSIS

Accurate diagnosis is based on:

- A detailed history & risk assessment
- A thorough physical examination
- Performing appropriate laboratory tests taking into account window periods
- Reviewing previous treatment & tests

History and physical examination are the basis of reaching a diagnosis in primary healthcare settings like in family physician clinics. Making a specific aetiological diagnosis is usually possible in referral centres and hospitals with adequate laboratory backup.

It must be remembered that clinical syndromes (e.g. urethritis and genital ulcer disease) may be polymicrobial in aetiology. All patients with an STI should be screened for other infections; in particular, they should be offered tests for syphilis and HIV infection.

5. TREATMENT

Treatment regimens must be safe & efficacious, easy to comply with, affordable, preferably given in a single dose, easily administered; and ideally should be provided on the patient's initial visit.

Treatment may often be based on clinical diagnosis only e.g. urethral discharge, vaginal discharge, and genital ulcers. It is often not possible to have an aetiological diagnosis at the first visit. In these situations, it is important to ensure that the medications used are effective against the most common pathogens responsible for the syndrome. Wherever possible, an aetiological diagnosis should be confirmed by laboratory tests for prognostication.

6. SEXUAL HEALTH ADVICE & COUNSELLING

a) Prevention of disease transmission / partner management

All patients should be informed of the diagnosis, nature of treatment and expected outcome, the need to comply with and complete the treatment, reporting of side effects, and avoidance of sex until cured. In some cases, follow-up for tests-of-cure may be necessary. Contact(s) of patients should be advised to attend for screening / empiric treatment.

b) Prevention of further infection

Counselling skills, which include respect for privacy, compassion and a non-judgemental attitude, are essential for effective delivery of prevention messages.

All patients should be counselled on the methods of reducing their risk of acquiring an STI/HIV in future, including secondary abstinence, reducing the number of sexual partners (especially concurrency) and avoiding sexual contact with persons who have multiple sexual partners.

They should be instructed on the correct and consistent use of condoms for oral, vaginal, and anal sex. The following recommendations ensure the proper use of male condoms:

- Use a new condom with each sex act (e.g., oral, vaginal, and anal).
- Carefully handle the condom to avoid damaging it with fingernails, teeth, or other sharp objects (e.g. orthodontic braces).
- Put the condom on after the penis is erect and before any oral or genital/anal contact with the partner.
- Use only water-based or silicone-based lubricants with latex condoms. Oil-based lubricants (e.g. Vaseline, massage oils, body lotions and creams) will weaken latex & should NOT be used.
- Ensure adequate lubrication during vaginal and anal sex, which might require the use of water-based lubricants.
- During withdrawal. to prevent the condom from slipping off, hold the condom firmly against the base of the penis and ideally withdraw while the penis is still erect.

Patients should be advised to seek medical attention if they feel that they have been exposed to an infection e.g. inadvertent unprotected sex, condom accidents etc. They should not self-medicate or seek treatment from unqualified persons.

Patients with multiple episodes of STIs should receive specific intensive counselling on strategies to reduce risk.

At-risk communities with substantial risk of HIV infection should also receive counselling on the option and efficacy of pre-exposure prophylaxis against HIV infection.

7. NOTIFICATION OF INFECTIONS

Certain STIs are notifiable in Singapore. Reporting of STIs and HIV/AIDS allows for accurate monitoring of disease epidemiology; and is needed for monitoring and evaluating the National STI and HIV control programmes.

Except for HIV/AIDS, there is no need to include the name, identity number or address of the patient when notifying an STI; only demographic data (STI, age, gender, ethnicity, nationality) is required. As notifications of STIs are not meant for case detection or contact tracing, patient privacy and confidentiality is maintained.

Gonorrhoea, Chlamydia, and Syphilis (infectious, non-infectious and congenital) should be notified electronically using form MD 131 https://www.cdlens.moh.gov.sg/cdlens/ within 72 hours of diagnosis.

HIV infection and AIDS should be notified to NPHEU using form MD 131 electronically: https://www.cdlens.moh.gov.sg/cdlens/ within 72 hours of diagnosis.

Viral Hepatitis (A, B, C, others) infections should be notified to CDD, MOH using form MD131 electronically: https://www.cdlens.moh.gov.sg/cdlens/ within 72 hours of diagnosis.

8. PARTNER MANAGEMENT / CONTACT TRACING

The public health objectives of partner notification are: (1) to interrupt the transmission of the STI; (2) identify populations at risk; and (3) reduce the incidence of infection.

Individual's objectives are: (1) to identify people who may benefit from treatment and counselling; (2) provide individual counselling; and (3) to prevent complications.

Partner notification can be undertaken in any of these ways:

1. By the patient (patient referral);
2. By the health care worker (provider referral) using telephone, letter or home visit;
3. A combination of the two (conditional referral).

Maintaining the confidentiality of the index patient is paramount to successful contact tracing.

Patient delivered partner therapy (PDPT), the practice of providing antibiotic treatment for certain STIs to the index patient to pass on to their partners, is becoming more acceptable and may be an effective strategy to control STIs.

9. CHEMOPROPHYLAXIS

Pre-exposure prophylaxis (PrEP) with co-formulated tenofovir and emtricitabine (TDF/FTC) is highly effective in reducing the chances of contracting HIV infection. PrEP has been recommended by WHO since 2015 as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches. Please refer to the chapter on PrEP.

Blind treatment of an STI in asymptomatic persons is discouraged. There is no universally effective antimicrobial. Furthermore, chemoprophylaxis may suppress but not cure a STI. This may lead to complications, promote the development of resistant strains of microbes, and/or provide a false sense of security to the patient and lead to onward transmission of infection.

10. EPIDEMIOLOGIC TREATMENT

Treatment of sexual contacts of patients with a confirmed STI without first obtaining laboratory confirmation may be indicated in situations where the risks of complications are high (e.g. in pregnancy), or when the follow-up of the contact may not be guaranteed or possible. Recommended treatment regimens must be used in these situations.

11. FOLLOW-UP

Test-of-cure is not routinely recommended for all STIs: please refer to individual chapters. Regular screening is recommended thereafter especially if there are new partners or frequent partner change.

BACTERIAL VAGINOSIS

DEFINITION

Bacterial vaginosis (BV) is a condition resulting from replacement of the normal H_2O_2-producing *Lactobacillus* sp. in the vagina with high concentrations of anaerobic bacteria (e.g. *Prevotella* species, *Mobiluncus* species, *Gardnerella vaginalis*, *Ureaplasma urealyticum* and *Mycoplasma hominis*) leading to an increase in pH from less than 4.5 to as high as 7.0. It may arise and remit spontaneously in sexually active and non-sexually active women. The exact role of sexual transmission in the pathogenesis of BV vaginal dysbiosis is unclear.

CLINICAL FEATURES

BV may be asymptomatic or present with a fishy-smelling, thin homogenous vaginal discharge. Risk factors include:

- Vaginal douching
- Receptive cunnilingus
- Recent change of sex partner
- Smoking
- Presence of an STI

LABORATORY TESTS

- 3 out of 4 of the following Amsel criteria should be present:
- Thin homogenous vaginal discharge that coats the vaginal wall and vestibule
- pH of vaginal fluid >4.5
- Positive amine (fish-like) odour test ("whiff test") before or after addition of 10% KOH
- Presence of clue cells on microscopy of vaginal discharge

Note:

- Menses, semen, cervical secretions or douching may affect the pH
- A weakly positive "whiff test" may be produced by menstrual blood or semen
- Exclude trichomoniasis

Culture of *G. vaginalis* is not recommended because it can be cultured from the vagina of >50% asymptomatic women. Cervical cancer screening tests alone should not be used for BV diagnosis because of their low sensitivity and specificity.

An alternative test involves use of a gram-stain vaginal smear evaluated with the Hay/Ison criteria or the Nugent criteria. Commercial tests are also available.

All women with BV should be tested for other STIs and HIV.

COMPLICATIONS

BV has been associated with adverse pregnancy outcomes (e.g. premature rupture of membranes, chorioamnionitis, preterm labour and preterm birth). BV is also associated with endometritis, PID and vaginal cuff cellulitis after invasive procedures (e.g. uterine curettage, hysterectomy, endometrial biopsy).

There is increasing evidence that the presence of BV (or absence of vaginal lactobacilli) has been shown to increase a woman's risk of acquiring HIV, *N. gonorrhoeae*, *C. trachomatis* and HSV-2 via heterosexual intercourse.

TREATMENT

Indications for treatment:

1. All symptomatic women, pregnant or non-pregnant**. [A]**
2. Asymptomatic pregnant women with high risk for preterm delivery**. [A]**
3. Asymptomatic women before surgical procedures**. [A]**
4. Women who do not volunteer symptoms may elect to take treatment if offered. They may report a beneficial change in their discharge following treatment.

General Measures
Patients should be asked to avoid vaginal douching, use of shower gels, antiseptic agents or shampoos in the bath. **[C]**

Recommended Regimen(s)
1. Metronidazole 400-500mg orally BD x 5-7 days **[1a, A]**

or

2. Metronidazole 2g orally single dose **[1b, A]**

or

3. Clindamycin cream 2% one full applicator (5g) intravaginally at bedtime x 7 days **[1b, A]**

or

4. Metronidazole gel 0.75% one full applicator (5g) intravaginally daily x 5 days **[1b, A]**

Alternative Regimen(s)
1. Clindamycin 300mg orally BD x 7 days **[1b, A]**

or

2. Tinidazole 2g orally daily x 2 days **[1b, A]**

Note:
- Metronidazole 2g single dose therapy may be slightly less effective at 4 week follow up. **[Ib]**
- Patients should avoid consuming alcohol during treatment with metronidazole and for 24 hours thereafter.
- Clindamycin cream is oil-based and might weaken latex condoms and diaphragms.
- Non-antibiotic based treatment with probiotic lactobacilli or lactic acid preparations have not yielded consistently reproducible evidence of efficacy as treatments for BV and no recommendation on their use can be made at present.

CONSIDERATIONS IN PREGNANCY
Recommended Regimen(s)
1. Metronidazole 400-500mg orally BD x 7 days **[1b, A]**

or

2. Metronidazole 200mg orally TDS x 7 days **[1b, A]**

or

3. Clindamycin 300mg orally BD x 7 days **[1b, A]**

Note:
- Intravaginal clindamycin cream administered at 16-32 weeks' gestation has been associated with an increase in adverse events (e.g. low birthweight and neonatal infections). Therefore, intravaginal clindamycin cream should only be used during the first half of pregnancy.
- Data is conflicting regarding the usefulness of screening and treating low risk asymptomatic pregnant women. Metronidazole use in the first trimester of pregnancy has not been shown to be teratogenic or mutagenic. **[Ia]**
- Metronidazole enters breast milk and may affect its taste. The manufacturers recommend avoiding high doses if breastfeeding. Small amounts of clindamycin enter breast milk, therefore use an intravaginal treatment for lactating women. **[C]**
- Screening for and treating BV in patients undergoing a termination of pregnancy reduces the incidence of subsequent endometritis and PID. **[Ia]**

CONSIDERATIONS IN HIV INFECTION
BV tends to recur with a higher frequency in HIV-positive women. BV may be a risk factor for female to male HIV transmission. These patients should be treated with the same treatment regimens as for HIV-negative women.

RECURRENT BV
There are few published studies evaluating the optimal approach to women with frequent recurrences of BV. Two studies reported a high incidence of BV in female partners of lesbians with BV. **[II]**

Possible approaches are:
- Suppressive therapy: Metronidazole gel 0.75% twice weekly x 4-6 months. **[Ia]**
- Metronidazole 400mg orally BD x 3 days at the start and end of menstruation or metronidazole 2g orally monthly (combined with fluconazole 150mg as a single dose if there is a history of candidiasis also). **[Ia]**
- Maintenance therapy involving acetic acid vaginal gel use at the time of menstruation and following unprotected sexual intercourse. **[III]**
- Probiotic lactobacilli applied daily during week 1 and 3 may lower recurrence rates. **[IIa]**

FOLLOW-UP
Follow-up is not necessary if symptoms resolve. For high-risk pregnant women, a one-month follow-up visit is recommended to evaluate if treatment is successful. Alternative regimen can be given for recurrent disease.

Long term maintenance regimens are not recommended.

MANAGEMENT OF SEXUAL CONTACTS
No clinical counterpart is recognised in males and screening and treatment has not shown to be beneficial for the patient or the male partner. Although studies have reported a high incidence of BV in female partners of lesbian women with BV **[II]**, no studies have as yet investigated the value of treating partners of lesbian women simultaneously.

References:
1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. BASHH (2012). National Guideline for the Management of Bacterial Vaginosis.

CANDIDIASIS

DEFINITION

Genital candidiasis is the infection of the vulva, vagina, prepuce and glans penis by *Candida albicans* (80-92%) or occasionally by other Candida species (*C. glabrata, tropicalis, krusei, parapsilosis*), *Torulopsis* species, or other yeasts. It is not generally considered a sexually transmitted infection.

CLINICAL FEATURES

Female patients may complain of vulval pruritus and discharge. Non-specific symptoms include soreness, burning, dyspareunia and external dysuria. Male patients may complain of a penile rash. Examination reveals vulval erythema, fissuring, satellite lesions, and discharge is typically curdy but may be thin in females; or white/red patches on the glans penis in males.

Pre-disposing factors include diabetes mellitus, disturbance of vaginal flora e.g. through use of broad-spectrum antibiotics, immunosuppression e.g. oral corticosteroids, hyperoestrogenaemia (including hormone replacement therapy and combined oral contraceptive pills).

LABORATORY TESTS

- Gram-stain or wet mount (saline or 10% KOH) of swabs from the vulva/vaginal wall, or penis/prepuce will reveal budding yeast cells and pseudo-hyphae (sensitivity 60%)
- Vaginal pH 4-4.5
- Culture on Sabouraud media (isolation in the absence of symptoms and negative direct smear is not an indication for treatment)
- Serum IgG antibodies should not be used for diagnosis

DIAGNOSIS

Symptoms and signs of vulvo-vaginitis or balanoposthitis and demonstration of yeasts/pseudohyphae on wet mount or Gram-stain or positive culture.

TREATMENT

Treatment is indicated for symptomatic patients. It is not recommended for asymptomatic patients with a positive Gram stain or culture because 10-20% of women harbour Candida species or other yeasts in the vagina in the absence of symptoms.

General Measures

Vulval emollients and or topical antifungal/steroid creams may provide symptomatic relief for secondary associated vulval dermatitis. Avoid local irritants (e.g. perfumed products) and tight fitting clothing. **[IV, C]**

Uncomplicated vulvovaginal candidiasis (VVC)

Since all topical and oral azole therapies give a clinical and mycological cure rate of over 80% in uncomplicated acute vulvovaginal candidiasis, choice is a matter of personal preference, availability and affordability. Nystatin preparations give a 70-90% cure rate in this situation.

Topical Therapies

1. Clotrimazole vaginal pessary 200mg intravaginally daily x 3 days; or
   100mg daily x 7 days; or
   500mg single dose **[II, A**]

   or

2. Sertaconazole vaginal pessary 300mg intravaginally single dose **[II, A]**

   or

3. Nystatin pessary 100,000units intravaginally daily x 7 to 14 days **[II, A]**

Oral Therapies

1. Fluconazole 150mg orally single dose **[II, A]**

or

2. Itraconazole 200mg orally BD x 1 day **[II, A]**

Alternative Regimen(s)

1. Miconazole nitrate vaginal pessary 200mg daily x 3 days; or
   100mg daily x 7 days; or
   cream (2%) 5g intravaginally daily x 7 days **[II, A]**
2. Miconazole 1,200mg vaginal pessary x 1 day **[II,A]**
3. Clotrimazole pessary cream (1%) 5g intravaginally daily x 7 days **[II, A]**
4. Econazole nitrate pessary 150mg intravaginally nightly x 3 days **[II, A]**
5. Butoconazole 2% cream 5g intravaginally x 1 day **[II, A]**
6. Tioconazole ointment (6.5%) intravaginally 4.6g in a single application **[II, A]**

Note: The topically applied azole drugs are more effective than nystatin.

CONSIDERATIONS IN PREGNANCY

Symptomatic vulvovaginal candidiasis should be treated. Only topical azole therapy should be given. Longer courses may be necessary. Oral azole therapy is contraindicated. **[II, B]**

CONSIDERATIONS IN HIV INFECTION

Candidiasis tends to occur with a higher frequency and persistence in HIV-positive women and colonization rates correlate with the severity of immunosuppression. These patients should be treated with the same treatment regimens as for HIV-negative women.

RECURRENT VULVOVAGINAL CANDIDIASIS

This can be considered if there are 3-4 or more episodes of symptomatic vulvovaginal candidiasis annually. Patients must be evaluated for any predisposing factors e.g. uncontrolled diabetes mellitus, immunosuppression, corticosteroid and long-term antibiotic use, hyperoestrogenaemia (HRT, OCP). Repeated courses of treatment may be required. Infection by less susceptible yeasts e.g. *C. glabrata* may require a longer duration of therapy.

Systemic treatment may be indicated for resistant/recurrent candidiasis:

Induction Regimen(s)

1. Fluconazole 150mg orally every 72 hours x 3 doses **[Ib, A]**

or

2. Itraconazole 100mg orally BD x 1-3 days **[II, A]**

or

3. Topical imidazole therapy can be increased to 10-14 days according to symptomatic response **[IV, C]**

Maintenance Regimen(s)

1. Fluconazole 150mg orally once a week x 6 months **[Ib, A]**

or

2. Itraconazole 400mg orally once a month x 6 months **[II, B]**

or

3. Clotrimazole pessary 500mg intravaginally once a week x 6 months **[II, B]**

Caution: Oral azole therapy is contraindicated in pregnancy. There are anecdotal reports of oral contraceptive failure with prolonged oral azole therapy. The creams and suppositories are oil-based and may weaken latex condoms and diaphragms. There is the risk of idiosyncratic drug-induced hepatitis with itraconazole.

USE OF PROBIOTICS/ LACTOBACILLUS

Evidence does not support the use of oral or vaginal lactobacillus for the prevention of vulvovaginal candidiasis. Adverse effect from their use are extremely infrequent however, and some evidence shows that, compared with conventional treatment, the use of probiotics as an adjuvant therapy could increases the rate of short-term clinical and mycological cure and decrease the relapse rate at one month but this did not translate into a higher frequency of long-term clinical or mycological cure.

MANAGEMENT OF SEXUAL CONTACTS

There is no evidence to support the screening or treatment of asymptomatic male sexual partners. For symptomatic balanoposthitis, topical imidazole creams BD x 7 days will usually eradicate the infection.

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. BASHH (2019). National Guideline for the Management of Vulvovaginal Candidiasis. (updated Jan 2021)

3. Xie HY et al. Probiotics for vulvovaginal candidiasis in non-pregnant women. Cochrane Database Syst Rev. 2017 Nov 23;11

CHANCROID

DEFINITION

Chancroid is a sexually transmitted infection caused by the bacterium *Haemophilus ducreyi*. This infection was once one of the most common causes of genital ulcer disease in parts of the world like India and Southeast Asia, but the incidence has now decreased markedly. Chancroid cases are now only diagnosed sporadically. Patients infected may have a co-infection with syphilis or herpes.

CLINICAL FEATURES

Infection with *H. ducreyi* may present with an erythematous papule that rapidly progresses into a pustule, which erodes into an ulcer. Infected persons may have more than one ulcer, and the lesions are almost always confined to the genital area and its draining lymph nodes.

A typical chancroid ulcer is about 1 to 2 cm in diameter, but the size is variable, especially in HIV-infected patients. The ulcer is painful and has an erythematous base; the borders are clearly demarcated and sometimes undermined. The base of the ulcer is usually covered with a grey or yellow purulent exudate and bleeds when scraped.

The most common sites for chancroid are the prepuce, corona, or glans penis in men, and the labia, vaginal introitus, and perianal areas in women. Some cases of chancroid may go undiagnosed, especially in asymptomatic women with vaginal or cervical lesions.

The involved nodes may undergo liquefaction and present as fluctuant buboes. Most buboes arise one to two weeks after the appearance of the primary ulcer and are often quite painful. Untreated buboes may spontaneously rupture and discharge frank pus. Scarring may result despite successful therapy.

LABORATORY TESTS

- Culture for *H. ducreyi* of a smear from ulcer or aspirate from buboes (sensitivity <80%)
- Multiplex PCR detection (>95%)
- Direct microscopy of a smear from ulcer showing Gram-negative coccobacilli (arranged in “shoals of fish” pattern) has low sensitivity and is not recommended as a diagnostic test.

A “probable diagnosis” may be made clinically if patient has typical clinical presentation and after exclusion of syphilis and HSV infection.

TREATMENT

Recommended Regimen(s)

Local Treatment

- Saline wash
- Aspiration of fluctuant buboes from adjacent normal skin
- Careful incision and drainage for treating fluctuant buboes can also be effective and safe to avoid frequent needle re-aspiration

Systemic Treatment

1. Ceftriaxone 250mg IM single dose **[Ib, B]**

   or

2. Azithromycin 1g orally single dose **[Ib, A]**

   or

3. Ciprofloxacin 500mg orally BD x 3 days* **[Ib, B]**
   Ciprofloxacin is contraindicated in pregnant and lactating women.

   or

4. Erythromycin base or stearate 500mg orally QDS x 7 days* **[Ib, B]**

*__Note__: The latter two regimens are recommended for HIV-positive patients rather than the single dose treatments.

***Not recommended**:* Tetracyclines and Ampicillin

Other Management Considerations
Patients who are uncircumcised and patients with HIV infection do not respond as well to treatment as those who are circumcised or HIV-negative. Patients should be tested for HIV infection at the time chancroid is diagnosed. Patients should be retested for syphilis and HIV 3 months after the diagnosis of chancroid if the initial test results were negative.

FOLLOW-UP
Chancroid ulcers usually begin to heal within 3 days of treatment and should heal completely by 7-14 days. Large ulcers might require >2 weeks for complete healing. If there is no improvement by 7 days, the patient should be re-evaluated for:

- Compliance with medication
- Co-infection with another STI
- Co-infection with HIV
- Non-STI ulcer disease
- Resistant organism

Inguinal lymphadenopathy will take a longer time to resolve than that of ulcers. In advanced cases, scarring may result despite eradication of infection.

MANAGEMENT OF SEXUAL CONTACTS
Sex partners should be examined and treated when indicated if they had sexual contact with the patient 10 days even in the absence of symptoms, as asymptomatic carriage of *H. ducreyi* may occur, but screening is not recommended.

CONSIDERATIONS IN PREGNANCY
Ciprofloxacin is contraindicated during pregnancy and lactation. No adverse effects of chancroid on pregnancy outcome have been reported so far.

CONSIDERATIONS IN HIV INFECTION
HIV-infected patients who have chancroid should be monitored closely because, as a group, these patients are more likely to experience treatment failure and to have ulcers that heal more slowly. HIV-infected patients may require longer courses of therapy than those recommended for HIV-negative patients, and treatment failures can occur with any regimen.

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. BASHH/IUSTI (2017). National Guideline for Management of Chancroid. (updated Jan 2021)

CHLAMYDIA TRACHOMATIS

DEFINITION

Chlamydia trachomatis is a bacterium which causes a variety of genito-urinary infections, depending on the serotypes. Chlamydial genital infections occur frequently among sexually active adolescents and young adults.

CLINICAL FEATURES

Many adult genital infections and most pharyngeal and rectal infections caused by chlamydia are asymptomatic.

Serotypes D to K cause non-gonococcal urethritis, mucopurulent cervicitis, orchitis and proctitis.

Lymphogranuloma venereum (LGV) is caused by serotypes L1-L3 (see chapter on LGV).

Several important complications may result from chlamydial infections, including pelvic inflammatory disease, ectopic pregnancy and tubal infertility in women, epididymo-orchitis in males, and conjunctivitis and reactive arthritis in both sexes. Maternal-foetal transmission to new-borns during delivery may lead to neonatal conjunctivitis and pneumonia.

LABORATORY TESTS

- *Chlamydia trachomatis* is an intracellular organism, specimens must include epithelial cells and not exudates alone.

- Nucleic acid-based amplification tests (NAAT): most sensitive 90-95%, highly specific, gold standard; polymerase chain reaction (PCR) can be used to test a range of specimens (urine, urethral, cervical, rectal, pharyngeal).

- Females: cervical or vulvo-vaginal swabs are specimens of choice, followed by first void urine (FVU); males: FVU is as sensitive as urethral swabs; care with inhibitors with urine specimens; storing urine overnight at 40C or freeze-thawing may enhance sensitivity of urine specimens.

- NAATs may be used for conjunctival, pharyngeal and rectal specimens, although not all kits currently unlicensed for these sites.

- Medico legal cases: samples for NAAT should be taken from all the sites where penetration has occurred, a reactive NAAT result should ideally be confirmed using a different NAAT.

- Antigen detection methods: direct fluorescent antibody (DFA) sensitivity 50-90%; enzyme immunoassay (EIA) poor sensitivity 50-70%, specificity >95%, inexpensive, can be used for large numbers of specimens. FVU or urethral swabs can be used for males, endocervical swabs are preferred for women.

- Cell culture for chlamydia in McCoy cell monolayers, used to be the gold-standard, and it is fairly sensitive (70-80%) and 100% specific. However, it requires stringent cold-chain, costly, and is not readily available.

- Giemsa-stained direct smear for the inclusion bodies within infected cells is useful only for ocular infections.

- Serological tests are not useful to diagnose acute chlamydial infections due to cross-reactivity between chlamydial species, high prevalence of chlamydia antibodies in high risk populations, and the unpredictability of serological response and changes in titres of IgM and IgG antibodies in acute uncomplicated infections.

TREATMENT

Uncomplicated urethral, endocervical, pharyngeal or rectal infections in adults

Recommended Regimen(s)

1. Doxycycline 100mg orally BD x 7 days **[1a, A]**

Alternative Regimen(s)

1. Azithromycin 1g orally single dose **[1a, A]**
   *Azithromycin 1g STAT dose is no longer recommended as first-line treatment as its use has been associated with emergence of macrolide-resistant *M. genitalium*; it is also not recommended for rectal *C. trachomatis* infections.

or

2. Levofloxacin 500mg orally once daily x 7 days **[1b, A]**

or

3. Erythromycin 500mg orally QDS **[1b, A]**

or

4. Ofloxacin 200mg orally BD or 400mg orally daily x 7 days **[1b, A]**

***Not recommended**:* Ampicillin and Trimethoprim-Sulfamethoxazole

CONSIDERATIONS IN PREGNANCY

Risk factors for *Chlamydia trachomatis* infection during pregnancy include young age (<25 years), past history of other STIs, new sex partner within the last 3 months, and multiple sex partners. Pregnant women whose sexual partners have NGU should be examined, and screened for other STIs, and treated on epidemiological grounds.

Recommended Regimen(s)

1. Azithromycin 1g orally single dose **[1a, A]**

Alternative Regimen(s)

1. Amoxicillin 500mg orally TDS x 7 days **[1a, A]**

or

2. Erythromycin 500mg orally QDS x 7 days **[1a, A]**

Note: Tetracyclines and ofloxacin are contraindicated during pregnancy.

NEONATAL CHLAMYDIA TRACHOMATIS CONJUNCTIVITIS

The other differential diagnoses of conjunctivitis in infants are gonococcal ophthalmia neonatorum, pyogenic and enteric Gram-negative conjunctivitis.

Diagnosis is made by culture or non-culture tests on specimens taken from the everted eyelid. Systemic treatment is essential to prevent complications such as chlamydia pneumonitis. Topical therapy alone is not adequate and unnecessary when systemic treatment is used. All neonates should be referred to an ophthalmologist ideally.

Recommended Regimen(s)

1. Syrup Erythromycin 50 mg/kg/day orally in 4 divided doses x 14 days

An association between oral erythromycin and infantile hypertrophic pyloric stenosis (IHIS) has been reported in infants aged <6 weeks who were treated with this drug. Infants treated with erythromycin should be followed for signs and symptoms of IHPS.

Mothers of infected infants and their sex partners should be screened and treated on epidemiological grounds. Follow up to determine resolution is recommended. The efficacy of erythromycin treatment is approximately 80%; a second course of therapy may be required.

CHLAMYDIA TRACHOMATIS PNEUMONIA IN INFANTS

Characteristic signs include a repetitive staccato cough and hyperinflation and bilateral diffuse infiltrates on CXR. Wheezing is rare, and infants are often afebrile. Diagnosis is made by culture or non-culture tests on specimens taken from the nasopharynx or tracheal aspirates.

Recommended Regimen(s)

1. Syrup Erythromycin 50 mg/kg/day orally in 4 divided doses x 14 days.

Mothers of infected infants and their sex partners should be screened and treated on epidemiological grounds. Follow up to determine resolution is recommended. The efficacy of erythromycin treatment is approximately 80%; a second course of therapy may be required.

CHLAMYDIA TRACHOMATIS PELVIC INFLAMMATORY DISEASE AND EPIDIDYMO-ORCHITIS

Recommended Regimen(s)

1. Doxycycline 100mg orally BD x 14 days **[III, B]**

or

2. Ofloxacin 400mg orally BD x 14 days **[III, B]**

FOLLOW-UP

- A test-of-cure is not necessary with compliance to treatment with a tetracycline or azithromycin has been completed, unless symptoms persist or reinfection is suspected.
- Test-of-cure is however recommended after 4 weeks for infections in infants, children and pregnant women, or when erythromycin was used.
- Non-culture tests (e.g. NAATs) performed within 4 weeks of completing treatment may yield false positive tests due to persistence of chlamydial antigens.
- Owing to the increased risk of complications following repeat infection in females, rescreening for reinfection may be indicated especially for high-risk females after 3 to 4 months.
- Serologic tests for Syphilis and HIV should be performed; if negative they should be repeated at 3 months for Syphilis and HIV, after the last risky exposure.

MANAGEMENT OF SEXUAL CONTACTS

Sex partners of symptomatic male patients within the last 60 days (or the most recent sex partner if the last contact was >60 days) should be screened and treated for chlamydial infection epidemiologically. The look-back period for contacts of female patients and asymptomatic males is longer, e.g. 3 months.

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. Lau A et al Azithromycin or Doxycycline for Asymptomatic Rectal Chlamydia trachomitis N Engl J Med 2021; 384: 2418-27

3. BASHH (2015). National Guideline for the Management of Genital Tract Infection with Chlamydia Trachomatis. (updated Sep 2018)

4. Johnson, R.E., Newhall, W.J., Papp, J.R., Knapp, J.S., Black, C.M., Gift, T.L., et al. (2002). Screening tests to detect Chlamydia trachomatis and Neisseria gonorrhoeae infections. (Vol 51, RR-15: 1-38). Retrieved from http://www.cdc.gov/std/labguidelines/rr5115.pdf

5. Lau, C.Y., & Qureshi, A.K. (2002). Azithromycin versus Doxycycline for Genital Chlamydial Infections: A Meta-Analysis of Randomized Clinical Trials. PubMed, 29(9):497-502.

GONORRHOEA

DEFINITION

Gonorrhoea is caused by the Gram-negative bacterium *Neisseria gonorrhoeae* (gonococcus, GC). The sites of infection include the urethra, the endocervix, the pharynx, the rectum, and also the conjunctiva.

CLINICAL FEATURES

Gonorrhoea is characterised clinically by a profuse purulent discharge from the affected genital site (>80% in male urethritis, up to 50% in female cervicitis), often accompanied by local pain or discomfort. However, asymptomatic infection may occur in 10% of urethral infections, >50% of cervical infections and >90% of pharyngeal and rectal infections. Contiguous spread of the infection may lead to epididymo-orchitis, prostatitis, endometritis and salpingo-oophritis. Haematogenous spread results in disseminated gonococcal infection (DGI).

LABORATORY TESTS

- A presumptive diagnosis of gonorrhoea is made on finding Gram-negative intracellular diplococci in a smear of the discharge.
    - In men, microscopy of urethral smears is more sensitive in symptomatic (90-95%) than asymptomatic (50-75%) patients.
    - In women, the sensitivity of microscopy of Gram-stained endocervical smears is around 50%. Microscopy is less sensitive for pharyngeal and rectal specimens.
- Confirmatory diagnosis is made by identification of the organism on culture media (e.g. modified Thayer-Martin agar).
- NAATs (PCR) are more sensitive than culture and can be used as diagnostic/screening tests on non-invasively collected specimens (urine and self-taken vaginal/pharyngeal/rectal swabs). The sensitivity of NAATs >90% for genital sites.
    - There are currently no NAATs licensed for use with conjunctival, pharyngeal or rectal samples, although studies suggest that the sensitivity of NAATs at non-genital sites exceeds 90% whereas the sensitivity of culture can be less than 60% for rectal swabs and less than 50% for pharyngeal swabs.
- The DSC clinic currently uses PCRs to detect urethral and cervical, pharyngeal and rectal GC.
- Some degree of caution is required in the interpretation of positive results as the specificity of NAATs is not 100%, especially if the risk profile of the patient is at odds with the result. Confirmation of a NAAT-positive result by culture can be considered in cases where there is some doubt. However, generally NAATs are considered reliable for detection.
- Because non-culture tests cannot provide anti-microbial susceptibility results, in cases of persistent gonococcal infection after treatment or potential resistant infections, clinicians should perform both culture and anti-microbial susceptibility testing.
- Gonococcal complement fixation test (GC-CFT) should not be used for diagnosing gonorrhoea.

SPECIMEN COLLECTION

Males:

Routinely from the urethra; oropharyngeal and/or rectal swabs when indicated by sexual history. First void urine provides alternative specimen for testing with a NAAT.

Females:

Routinely from endocervix if speculum examination performed; rectal and oropharyngeal tests and when indicated by the sexual history. Urine or self-taken vaginal swabs are suitable specimens for screening tests using a NAAT.

TREATMENT

Uncomplicated infection in adults: urethral, endocervical and rectal infection

Recommended Regimen(s)

1. Ceftriaxone 500mg IM single dose *plus* doxycycline 100mg orally BD x 7 days

Alternative Regimen(s)

1. Aztreonam 1g IM single dose *plus* doxycycline 100mg orally BD x 7 days
   **Aztreonam has been used in patients at the DSC clinic when other alternatives are not available*

or

2. Gentamicin 240mg IM single dose *plus* doxycycline 100mg orally BD x 7 days

or

3. Spectinomycin 2g IM single dose (less easily available)
   plus doxycycline 100mg orally BD x 7 days

It is important to emphasize that treatment of GC should be accompanied with anti-chlamydia therapy (e.g. doxycycline). This treats potential concurrent infection. However, please note that there is evidence to suggest that the empirical use of azithromycin is potentially contributing to resistant *Mycoplasma genitalium* strains.

Note: The fluoroquinolones (e.g. ciprofloxacin, ofloxacin, norfloxacin) are contraindicated as >80% of isolates in Singapore and the region are resistant.

CONSIDERATIONS IN PREGNANCY

- Cephalosporins in the recommended dosages are safe and effective in pregnancy.
- Spectinomycin can be administered to women who are unable to tolerate cephalosporins.
- Simultaneous treatment for chlamydial infection with azithromycin 1g orally in a single dose is advocated.

Recommended Regimen(s)

Pharyngeal infection

1. Ceftriaxone 500mg IM single dose with doxycycline 100mg BD x 7 days

Disseminated Gonococcal Infection (DGI)

Hospitalisation under specialist care is recommended.

1. Ceftriaxone 1g IM or IV daily *plus* doxycycline 100mg orally BD x 7 days

or

2. Cefotaxime 1g IV every 8 hours *plus* doxycycline 100mg orally BD x 7 days

or

3. Spectinomycin 2g IM every 12 hours *plus* doxycycline 100mg orally BD x 7 days

Therapy should continue for 24-48 hours after improvement begins, and can be converted to an oral cephalosporin therapy for a total of 7 days. Anti-chlamydia therapy should be given at the same time.

Gonococcal Acute Epididymitis and Epididymo-Orchitis

1. Ceftriaxone 500mg IM daily x 1-3 days + doxycycline 100mg orally BD x 2 weeks

Adult Gonococcal Ophthalmia

1. Ceftriaxone 1g IM single dose with doxycycline 100mg orally BD x 7 days
   plus
   lavage of the infected eye with normal saline

Topical antibiotics alone do not eradicate the infection and rigid adherence to topical therapy is not essential. All patients should be referred for ophthalmologic assessment.

Neonatal gonococcal ophthalmia
Lavage of the infected eye with normal saline *and*

1. Ceftriaxone 25-50 mg/kg IM, with single dose not to exceed 125 mg

or

2. Cefotaxime 100 mg/kg IM single dose.

Topical antibiotics alone do not eradicate the infection. All patients should be referred for ophthalmologic assessment.

Screen the mother and her sexual partner(s) for gonorrhoea and other STIs. The mother should be treated on epidemiological grounds.

Uncomplicated Gonococcal Infections in Older Children *(urethral, vulvovaginal, cervical, pharyngeal, rectal infections)*

Children who weigh >45kg or >12 years of age should be treated with adult regimens.

Children who weigh <45kg or <12 years of age should be treated as follows:

1. Ceftriaxone 25–50 mg/kg IV or IM in a single dose, not to exceed 250 mg IM
   plus

   Azithromycin 1g orally in a single dose (if >45kg)
   or
   Doxycycline 100mg orally BD x 7 days (if >45kg and >8 years old)

Not Recommended
The following medications are not recommended for treating gonococcal infection in Singapore as they are either ineffective or have not been adequately evaluated:

- Tetracyclines (they are given as part of anti-chlamydia therapy, not as primary treatment)
- Penicillins
- Early generation fluoroquinolones
- Erythromycin
- Trimethoprim/sulfamethoxazole

FOLLOW-UP

- At the DSC clinic, test-of-cure and assessment for post-gonococcal urethritis (PGU) is performed after 14 days
- Test-of-cure culture tests are recommended in all cases at all sites, especially for pharyngeal GC.
- In cases of possible antibiotic resistance, cultures should be performed with additional anti-microbial sensitivity.
- Patients with gonococcal ophthalmia should have cultures done daily while on therapy and again on the 5th and 14th days after completion of therapy.
- Serologic tests for syphilis and HIV should be performed; if negative they should be repeated at 3 months after the last at-risk exposure.

MANAGEMENT OF SEXUAL CONTACTS
Sexual contacts of the patients in the preceding 60 days should be traced, screened and treated on epidemiologic grounds. If the last sexual exposure was >60 days, the patient's most recent partner should be treated.

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. BASHH (2018). BASHH National Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults. (updated March 2020)

3. Kirkcaldy RD, Weinstock HS, Moore PC, et al. The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhea. Clin Infect Dis 2014;59:1083-91

FEMALE GENITAL SYNDROMES

MUCOPURULENT CERVICITIS

DEFINITION

Mucopurulent cervicitis (MPC) is defined as the presence of mucopurulent discharge from the endocervix, which appears yellow on a cotton-tipped swab. There is often oedema, erythema and contact bleeding of the cervix. A Gram-stained endocervical smear which shows ≥30 cells per high power field (1000X) is significantly correlated with gonococcal or chlamydial infection.

AETIOLOGICAL AGENTS

- *Neisseria gonorrhoeae*: gram-negative diplococci may be seen
- *Chlamydia trachomatis*
- *Mycoplasma genitalium*
- *Trichomonas vaginalis*
- *Herpes simplex virus*

TREATMENT

If *N. gonorrhoeae* is visualised on Gram-stain or detected on PCR:

- Treat as for uncomplicated gonorrhoea in adults with co-treatment for chlamydial infection

If *N. gonorrhoeae* is not visualised:

- Treat as for chlamydial infection with Doxycycline 100mg orally BD x 7 days

If *M. genitalium* is detected on PCR:

- Treat with Doxycycline 100mg orally BD x 7 days

  followed by
  Moxifloxacin 400mg orally daily x 7 days (refer to chapter on *M. genitalium*)

Note: Treatment of mucopurulent cervicitis in HIV-infected women is important because cervicitis increases cervical HIV shedding; treatment of this cervicitis reduces HIV shedding from the cervix and may reduce HIV transmission to susceptible sex partners.

FOLLOW-UP

Culture for test-of-cure 14 days after treatment for *N. gonorrhoeae*.

MANAGEMENT OF SEXUAL CONTACTS

Management of sex partners of women treated for MPC should be appropriate for the identified STI. All male sex partners within 60 days should be evaluated and treated for *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis* and *M. genitalium*.

References:

1. Bjornelius, E., Lidbrink, P., Jensen, J.S.(2000). Mycoplasma Genitalium in Non-gonococcal Urethritis - A Study in Swedish Male STD Patients. Int J STD AIDS, 11(5):292-6. Retrieved from, PubMed.

2. Manhart, L.E., Critchlow, C.W., Holmes, K.K., Dutro, S.M. Eschenbach, D.A., Stevens, C.E., Totten, P.A. (2004). Mucopurulent Cervicitis and Mycoplasma Genitalium. J Infect Dis, 190(4):866. Retrieved from, PubMed.

3. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

PELVIC INFLAMMATORY DISEASE

DEFINITION

Pelvic Inflammatory Disease (PID) is a clinical syndrome comprising of a spectrum of inflammatory disorders of the upper genital tract in women. PID usually results from infection ascending from the cervix causing endometritis, salpingitis, parametritis, oophoritis, tubo-ovarian abscess or pelvic peritonitis.

AETIOLOGICAL AGENTS

The aetiology of PID is often polymicrobial although pathogen-negative PID is common.

Sexually transmitted pathogens

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- *Mycoplasma genitalium*

Non-sexually transmitted pathogens

- Anaerobic bacteria
- *Gardnerella vaginalis*
- Other vaginal bacteria e.g. Gram-negative rods, streptococci

The insertion of an intrauterine device (IUD) increases the risk of developing PID but only for 4-6 weeks after insertion (risk probably highest in women with pre-existing gonorrhoea or chlamydia).

DIAGNOSIS

Diagnosis of PID is based on clinical signs and symptoms although they lack sensitivity and specificity compared to laparoscopy. The value of ultrasound scanning is also limited for uncomplicated PID but helpful if an abscess is suspected.

Testing for *N. gonorrhoeae*, *C. trachomatis* and *M. genitalium* (where available) in the lower genital tract is recommended as a positive test supports the diagnosis of PID. However, negative tests do not exclude PID.

Empirical treatment of PID should be started in sexually active women with recent onset of pelvic or lower abdominal pain (in whom pregnancy has been excluded and if no other cause for the pain can be identified) and if one or more of the following criteria are present on pelvic examination:

- Abdominal tenderness on palpation with or without rebound tenderness
- Cervical motion tenderness on bimanual vaginal examination
- Adnexal tenderness on bimanual vaginal examination

Additional criteria that support a diagnosis of PID include the following:

- Cervical infection with *N. gonorrhoeae*, *C. trachomatis* or *M. genitalium*
- Fever >38 °C
- Abnormal cervical or vaginal mucopurulent discharge
- Abnormal vaginal bleeding, including post-coital, intermenstrual bleeding and menorrhagia
- Deep dyspareunia
- Presence of WBCs on saline microscopy of vaginal secretions
- Elevated erythrocyte sedimentation rate or C-reactive protein
- Pelvic abscess or inflammatory complex detected by bimanual examination or by ultrasound

The most specific criteria for diagnosing PID include:

- Endometrial biopsy with histological evidence of endometritis
- Transvaginal ultrasound or MRI showing thickened, fluid filled tubes, with or without free pelvic fluid or tubo-ovarian complex
- Laparoscopic abnormalities consistent with PID

TREATMENT
The treatment regimens are empiric and should provide broad spectrum cover *for N. gonorrhoeae*, *C. trachomatis*, and a wide variety of aerobic and anaerobic bacteria.

1. Outpatient Treatment (for patients not requiring hospitalisation)
General Measures
- Rest and analgesia.
- Consider removing the IUD if there is no clinical improvement within 72 hours of initiating treatment, otherwise removal is not necessary. Treatment outcomes do not generally differ between women who retained the IUD and those who had it removed.
- To avoid reinfection patients should be advised to avoid oral or genital intercourse until they, and their partner(s), have completed treatment.

Recommended Regimen(s)
Delaying treatment increases the risk of long-term sequelae such as ectopic pregnancy, infertility and pelvic pain. Therefore, a low threshold for empiric treatment of PID is recommended.

1. Ceftriaxone 500mg IM single injection **[Ib, A]**
   plus
   Doxycycline 100mg orally BD x 14 days **[Ib, A]**
   plus
   Metronidazole 400mg orally BD x 14 days **[Ib, A]**

   or

2. Ofloxacin 400mg orally BD x 14 days
   or
   Levofloxacin 500mg orally once daily x 14 days **[Ib, A]**

   plus
   Metronidazole 400mg orally BD x 14 days **[Ib, A]**

   or

3. Moxifloxacin 400mg orally BD x 14 days **[Ib, A]**
   Moxifloxacin provides the highest microbiological activity against *M. genitalium* in patients who test positive.

Note:
Ofloxacin, levofloxacin and moxifloxacin should be avoided in patients who are at risk of gonococcal PID because of increasing quinolone resistance. These are effective for the treatment of *C. trachomatis*.

Ceftriaxone may be substituted by cefoxitin 2g IM with probenecid 1g orally, or cefotaxime 500mg IM with Probenecid 1g orally, or equivalent cephalosporin.

Replacing intramuscular ceftriaxone with an oral cephalosporin (e.g. cefixime) is not recommended (there is no clinical trial evidence to support its use, and tissue levels are likely to be lower).

The alternative regimen of ceftriaxone 500mg IM STAT, followed by azithromycin 1g/week orally for 2 weeks should be restricted to women who are known to be *M. genitalium* negative (to reduce macrolide induced resistance) and where recommended treatments are not appropriate.

2. Inpatient Treatment
This is indicated when:
- The diagnosis is uncertain
- Surgical emergencies e.g. appendicitis and ectopic pregnancies, cannot be excluded
- Suspected tubo-ovarian abscess
- The patient is pregnant
- Severe symptoms and signs (including nausea and vomiting) preclude outpatient treatment
- Poor response to previous antibiotics; or the patient is immunodeficient

Recommended Regimen(s)
Intravenous therapy should be continued until 24 hours after clinical improvement.

1. Ceftriaxone 2g IV daily
   plus
   Doxycycline 100mg IV BD (oral doxycycline may be used if tolerated)

   followed by
   Doxycycline 100mg orally BD x total 14 days
   plus
   Metronidazole 400mg orally BD x total 14 days **[Ib, A]**

or

2. Clindamycin 900mg IV TDS
   plus
   Gentamicin loading dose IV or IM 2mg/kg then maintenance 1.5mg/kg every 8 hours

   followed by
   Doxycycline 100mg orally BD x total 14 days
   or
   Clindamycin 450mg orally QDS x total 14 days

   and
   Metronidazole 400mg orally BD x total 14 days **[Ib, A]**

Alternative Regimen(s)

1. Ofloxacin 400mg IV BD x 14 days **[IIII, B]**
   plus
   Metronidazole 500mg IV TDS x 14 days **[III, B]**

or

2. Ciprofloxacin 200mg IV BD x 14 days **[III, B]**
   plus
   Doxycycline 100mg orally or IV BD x 14 days **[III, B]**
   plus
   Metronidazole 500mg IV TDS for 14 days **[III, B]**

Note: Pregnant women or HIV positive women with PID should be hospitalised and treated with parenteral antibiotics.

FOLLOW-UP
Review at 72 hours is recommended especially for those with moderate or severe symptoms or signs. Lack of improvement suggests the need for further investigation, parenteral therapy and/or surgical intervention.

Further review 2-4 weeks after therapy is recommended to ensure adequate clinical response, treatment compliance, treatment of contacts, repeat pregnancy test if indicated, and test of cure.

Tests of cure are recommended as follows if initial tests are positive:

- 2 weeks after treatment for *N. gonorrhoeae*
- 3-5 weeks after treatment for *C. trachomatis* in women who have persisting symptoms or if concerns with treatment compliance or risk of persisting or reinfection
- 4 weeks after treatment for *M. genitalium*

MANAGEMENT OF SEXUAL CONTACTS

Male partners of women with STI positive PID are often asymptomatic. Partners who had sexual contact with the patient during the 60 days before the onset of symptoms (or most recent sex partner if last sexual intercourse was >60 days) should be screened for STIs and empirically treated with regimens effective against relevant pathogens (*N. gonorrhoeae, C. trachomatis* and *M. genitalium*).

Because many cases of PID are negative for *N. gonorrhoeae, C. trachomatis* or *M. genitalium*, broad spectrum empirical therapy should be offered to male partners, e.g. doxycycline 100mg orally BD x 7 days.

References:

1. BASHH.(2018). National Guideline for the Management of Pelvic Inflammatory Disease. Retrieved from http://www.bashhguidelines.org/media/1170/pid-2018.pdf

2. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

VULVOVAGINITIS

INTRODUCTION

The symptoms of vaginitis include vaginal discharge, vulval itch or irritation and vaginal odour. Clinically, there may be an abnormal vaginal discharge, vaginal and vulval erythema and/or oedema.

AETIOLOGICAL AGENTS

- *Trichomonas vaginalis*
- *Candida albicans*
- *Gardnerella vaginalis* and anaerobic organisms

INVESTIGATIONS

1. pH of the vaginal discharge
2. Microscopic examination of a wet mount and Gram-stain specimen of vaginal fluid
3. Whiff test (a fishy odour after the addition of 10% KOH to the vaginal discharge)
4. PCR for Trichomonas / Gardnerella (if available)

TREATMENT

See guidelines on management of trichomoniasis, vulvovaginal candidiasis and bacterial vaginosis.

GRANULOMA INGUINALE (DONOVANOSIS)

DEFINITION

It is a sexually transmitted infection caused by the gram-negative bacillus *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*). This infection is rarely seen locally but endemic in India, parts of South America and South Africa.

CLINICAL FEATURES

Presents with painless "beefy" red (highly vascular) granulomatous genital ulcers which bleed easily without regional lymphadenopathy. Other clinical presentations are nodular, hypertrophic, necrotic, and sclerotic types. The lesions may develop secondary bacterial infection or may be co-infected with another STI.

LABORATORY TESTS

- Tissue smears from ulcer to reveal intra-cellular Donovan bodies (Giemsa, Wright's or silver stains) with "safety-pin" bipolar staining, found within histiocytes.
- Biopsy of the ulcer to reveal granulomas and Donovan bodies
- Donovan bodies are characterised by:
    - Location within large (20-90µm) histiocytes
    - Pleomorphic appearance 1-2 x 0.5-0.7µm
    - Bipolar densities and a capsule often visible
    - Stain Gram negative
- Culture is difficult
- There are currently no FDA approved PCR kits for diagnosis

TREATMENT

Local Treatment

Normal saline wash

Systemic Treatment

Recommended Regimen(s)

1. Azithromycin 1g orally once a week or 500mg daily x at least 3 weeks; and until all lesions have completely healed

Alternative Regimen(s)

1. Doxycycline 100mg orally BD x at least 3 weeks and until all lesions have completely healed

or

2. Erythromycin 500mg orally QDS x at least 3 weeks and until all lesions have completely healed

or

3. Trimethoprim-sulfamethoxazole (160mg/800mg) tablet orally BD x at least 3 weeks and until all lesions have completely healed

or

4. Ciprofloxacin 750mg orally BD x at least 3 weeks and until all lesions have completely healed

or

5. Gentamicin 1mg/kg IV every 8 hours can be added to any of the above regimens if patient is not responding to treatment.

Addition of another antibiotic may be considered if improvement is not evident within the first few days of therapy.

FOLLOW-UP
If the treatment is effective, clinical response is evident within 7 days. Treatment should be continued until ulcers heal completely. Relapse can occur 6-18 months after apparently effective therapy.

MANAGEMENT OF SEXUAL CONTACTS
Persons who have had sexual contact with a patient who has granuloma inguinale within 60 days before onset of the patient's symptoms should be examined and offered therapy. However, the value of empiric therapy in the absence of clinical signs and symptoms has not been established.

CONSIDERATIONS IN PREGNANCY
Pregnancy is a relative contraindication to the use of sulphonamides. Pregnant and lactating women should be treated with erythromycin, and consideration should be given to the addition of a parenteral aminoglycoside (e.g. gentamicin). Azithromycin may be useful for treating granuloma inguinale in pregnancy. Doxycycline and ciprofloxacin are contraindicated in pregnant women.

CONSIDERATIONS IN HIV INFECTION
Persons with both granuloma inguinale and HIV infection should receive the same regimens as those who are HIV negative. Consideration should be given to the addition of a parenteral aminoglycoside (e.g. gentamicin).

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. BASHH (2018). National Guideline for the Management of Donovanosis (Granuloma Inguinale) (updated Jul 2019)

HERPES SIMPLEX VIRUS

DEFINITION

Genital herpes is a chronic, life-long viral infection. Two types of DNA Herpes simplex virus (HSV) can cause genital herpes: HSV-1 and HSV-2. Most cases of recurrent genital herpes are caused by HSV-2, but an increasing proportion has been attributed to HSV-1 infection, especially among MSM and young women. HSV-1 is now the most common cause of genital herpes in some countries. Transmission of the virus can occur through genital to genital, mouth to genital, genital to anal and mouth to anal contact.

CLINICAL FEATURES

First-episode genital herpes may either be primary or non-primary. Primary genital herpes is defined as infection occurring in persons with no prior exposure to either HSV type 1 or 2. Non-primary genital herpes is defined as the first-genital episode in persons who have evidence of prior HSV infection at another body site with either HSV type 1 or 2.

First-episode genital herpes is often severe, presenting with multiple grouped vesicles, which rupture easily leaving painful erosions and ulcers. In the male, the lesions occur mainly on the prepuce and sub-preputial areas of the penis; in the female, on the vulva, vagina and cervix. Healing of uncomplicated lesions take 2 to 4 weeks. Complications may include aseptic meningitis, autonomic neuropathy resulting in urinary retention and autoinoculation to fingers.

Recurrent attacks are usually less severe than the first episode. The vesicles or erosions develop on a single anatomical site and these usually heal within 10 days. Median recurrence rate is approximately four recurrences per year for HSV-2 and is four times more frequent than the recurrence rate for HSV-1.

The majority of persons with HSV infection has mild, often unrecognised or sub-clinical disease and is unaware of the infection (asymptomatic carriers). They may nevertheless shed the virus intermittently in the genital tract and thus transmit the infection to their partners unknowingly.

HSV is a significant cause of proctitis in MSM, more commonly found in HIV-positive than HIV-negative MSM. Only 32% of MSM with HSV-associated proctitis had visible external anal ulceration.

A patient's prognosis and the type of counselling needed depend on the type of genital herpes (HSV-1 or HSV-2) causing the infection. Therefore, the clinical diagnosis of genital herpes should be confirmed by laboratory testing.

LABORATORY INVESTIGATIONS

Nucleic acid amplification methods (NAATs) including PCR assays for HSV DNA

Rapid, sensitive and highly specific, allows viral typing. NAATs are recommended as the preferred diagnostic method for genital herpes. PCR is the test of choice for diagnosing HSV infections affecting the CNS and systemic infections (e.g. meningitis, encephalitis, and neonatal herpes).

Viral isolation in cell culture

The sensitivity of viral culture is low, especially for recurrent lesions, and declines as the lesions begin to heal. Specificity is nearly 100%, with viral typing possible.

Type-specific serological tests (TSSTs)

Based on recombinant type-specific glycoproteins gG1 (HSV-1) and gG2 (HSV-2). The detection of HSV-1 IgG or HSV-2 IgG or both represents HSV infection at some point in time. Caution is needed when interpreting serology results. Routine screening for HSV antibodies is not indicated.

Serology may be useful in certain clinical situations:

- Recurrent genital symptoms or atypical symptoms with negative HSV PCR or culture
- Clinical diagnosis of genital herpes without laboratory confirmation
- Asymptomatic partners of serodiscordant couples of genital herpes, including women who are planning for pregnancy or are pregnant
- STI evaluation for persons with multiple sex partners, persons with HIV infection and MSM at increased risk for HIV acquisition

- Pregnant mothers presenting with first episode of genital herpes in the third trimester (see section below on “Management of genital herpes in pregnancy”)

As nearly all HSV-2 infections are sexually acquired, the presence of type-specific HSV-2 antibody implies anogenital infection. Most persons with HSV-1 antibodies have oral HSV infection acquired during childhood, which might be asymptomatic. The presence of HSV-1 antibody does not distinguish anogenital from orolabial infection.

TREATMENT

General Measures

- Cleaning of the affected areas with normal saline
- Analgesia
- Treatment of any secondary bacterial infection.

Specific Therapy

Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued.

In view of HSV being a common cause of proctitis in MSM, clinicians should consider empirical treatment for HSV in the presence of symptomatic proctitis. Antiviral treatment is as for genital herpes.

Topical therapy is of limited value for genital herpes and is <u>not indicated</u> if systemic therapy is administered.

Recommended Regimen(s)

<u>First-episode genital herpes</u>

1. Acyclovir 400mg orally TDS x 7-10 days **[Ib, A]**

or

2. Valacyclovir 1g orally BD x 7-10 days **[Ib, A]**

or

3. Famciclovir 250mg orally TDS x 7-10 days **[Ib, A]**

For optimal benefit, the treatment should be started within 48 to 72 hours of onset of lesions, when new lesions continue to form or when symptoms and signs are severe. Treatment can be extended if healing is incomplete after 10 days of therapy.

<u>Recurrent genital herpes</u>

Most recurrent attacks are mild and can be managed with general measures only. Routine use of specific treatment is not necessary. Management should be decided together with the patient.

<u>Episodic Treatment</u>

Effective episodic treatment of recurrent herpes requires initiation of therapy within 1 day of lesion onset or during the prodrome that precedes some outbreaks. The patient should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin.

1. Acyclovir 400mg TDS or 800mg orally BD x 5 days **[Ib, A]**

or

2. Acyclovir 800mg orally TDS x 2 days **[Ib, A]**

or

3. Valacyclovir 500mg orally BD x 3 days **[Ib, A]**

or

4. Valacyclovir 1g orally daily x 5 days **[Ib, A]**

or

5. Famciclovir 125mg BD x 5 days **[Ib, A]**

or

6. Famciclovir 1g BD x 1 day **[Ib, A]**

Suppressive Treatment

Suppressive therapy reduces the frequency of genital herpes recurrences and may be considered in patients who have frequent recurrences (i.e. 6 or more recurrences per year). Suppressive therapy has the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners.

1. Acyclovir 400mg orally BD **[Ib, A]**

or

2. Valacyclovir 500mg orally daily **[Ib, A]**

or

3. Valacyclovir 1000mg orally daily (for ≥10 recurrences in 1 year) **[Ib, A]**

or

4. Famciclovir 250mg orally BD **[Ib, A]**

Physicians should stop treatment after 9 to 12 months to see if the recurrence rate warrants continued prophylaxis.

FOLLOW-UP

Counselling of infected persons and their sex partners is critical to the management of genital herpes. The goals of counselling are to help patients cope with the infection and prevent sexual and perinatal transmission.

The following should be discussed:

- Information on the natural history of the disease, potential for recurrent attacks, role of asymptomatic shedding in sexual transmission
- Abstinence from sexual activity during prodromal symptoms or when lesions are present
- Advice to inform current and new sexual partners of genital herpes
- Use of condoms with new or uninfected partners may reduce, but not eliminate risk of transmission, particularly in the first 12 months after the first attack
- Sexual relationships and transmission to partners
- Information on anti-viral treatment available
- Increased risk of HIV acquisition among HSV-2 seropositive persons who are exposed to HIV
- Ability to bear healthy children
- Risk of neonatal infection: women with a history of genital herpes or whose partners have a history of genital herpes should inform their obstetrician early in pregnancy
- The misconception that HSV causes cancer should be dispelled.

MANAGEMENT OF SEXUAL CONTACTS

Sexual partners of patients with genital herpes are likely to benefit from evaluation and counselling. They should be questioned on a history of typical and atypical genital lesions, encouraged to examine themselves for lesions and seek medical attention early if lesions appear. TSSTs may be useful in counselling couples.

CONSIDERATIONS IN HIV INFECTION

Genital herpes is common in HIV infected individuals and might be severe, painful and atypical. HSV shedding is increased in persons with HIV infection, even with anti-retroviral therapy which reduces the severity and frequency of symptomatic HSV genital herpes.

In patients with advanced HIV, double the standard dose of antiviral should be considered, keeping in mind the potential risk of renal impairment.

Acyclovir Resistance

Acyclovir-resistant strains, which usually lack the thymidine kinase enzyme, have been reported in patients with concurrent HIV infection. Acyclovir-resistant strains will also be resistant to valacyclovir and famciclovir. IV foscarnet (40-80mg/kg IV every 8 hours till clinical resolution) or IV cidofovir (5mg/kg once weekly) are often effective. Topical cidofovir or imiquimod may be applied to lesions once daily for 5 consecutive days as topical alternatives. Complex cases should be co-managed with an infectious disease specialist.

Recurrent Episodic Treatment

1. Acyclovir 400mg orally TDS x 5-10 days **[IV, C]**

or

2. Valacyclovir 1g orally BD x 5-10 days **[IV, C]**

or

3. Famciclovir 500mg orally BD x 5-10 days **[IV, C]**

Suppressive Treatment

1. Acyclovir 400-800mg orally BD or TDS **[IV, C]**

or

2. Valacyclovir 500mg orally BD **[IV, C]**

or

3. Famciclovir 500mg orally BD **[IV, C]**

CONSIDERATIONS IN PREGNANCY

Factors associated with transmission include the type of maternal infection (primary or recurrent), presence of transplacental maternal neutralizing antibodies, duration of rupture of membrane before delivery, mode of delivery and use of foetal scalp electrodes.

The risk of transmission to neonate during vaginal delivery is highest (30-50%) from a mother with primary genital herpes in the third trimester, particularly within 6 weeks of delivery. It is much lower (0-3%) for mothers with recurrent herpes, even if lesions are present at time of delivery.

The safety of systemic acyclovir, valacyclovir and famciclovir during pregnancy is not yet established (all US FDA class B). Current findings do not show an increased risk for major birth defects after acyclovir treatment in the first trimester. Safety data for acyclovir may be extrapolated with valacyclovir in late pregnancy, but as there is less experience with valacyclovir or famciclovir, they are not recommended as first line treatment.

First-Episode Genital Herpes: 1st and 2nd trimester acquisition

- There is no evidence of increased risk of miscarriage or increased incidence of congenital abnormalities with primary genital herpes in the first trimester.
- The diagnosis of genital herpes should be confirmed by viral PCR, and treatment should not be delayed. Usually oral acyclovir in standard doses (400mg TDS x 5 days) or IV for disseminated HSV infection.
- Daily suppressive acyclovir 400mg TDS from 36 weeks of gestation reduces HSV lesions at term and hence the need for delivery by caesarean section. This increase from the standard suppressive dose is recommended in view of the greater volume of drug distribution during pregnancy.
- Vaginal delivery is anticipated in women who present with first episode genital herpes in the first and second trimesters as the risk for transmission to the neonate at delivery is low. **[IV, C]**

First-Episode Genital Herpes: 3rd trimester acquisition

- There is some evidence of increased perinatal morbidity (preterm labour and low birthweight), together with stillbirth, however the data are conflicting.
- Treatment should not be delayed and usually involve the use of oral acyclovir in standard doses (400mg TDS x 5 days) or IV for disseminated HSV infection.
- In the third trimester, treatment will usually continue with daily suppressive acyclovir 400mg TDS until delivery.
- Caesarean section should be recommended to all women presenting with first-episode genital herpes lesions in the third trimester, particularly within 6 weeks of the expected date of delivery. **[IIb, C]**
- As it may be difficult to distinguish between primary and recurrent genital HSV infections, use of TSST serology is advisable. Characterising the infection will influence the advice given regarding mode of delivery and risk of neonatal herpes infection. The presence of antibodies of the same type as HSV isolated from genital swabs would confirm a recurrence rather than primary infection and elective caesarean section would not be indicated. However, if results are not available, the initial plan of delivery should always be based on the assumption that all first-episode lesions are primary genital herpes. **[IV,C]**

Recurrent Genital Herpes in Pregnancy

- The risk of neonatal herpes for mothers with recurrent genital herpes is low, even if lesions are present at time of delivery (0-3% for vaginal delivery). **[III, C]** Vaginal delivery should be anticipated.
- Daily suppressive acyclovir 400mg TDS should be considered from 36 weeks of gestation.
- Sequential PCR culture during late gestation to predict asymptomatic viral shedding at term, or at delivery is not indicated.

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

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HIV POST-EXPOSURE PROPHYLAXIS (PEP)

INTRODUCTION

Antiretroviral therapy (ART) offered as PEP has become the standard of care for healthcare workers who have had occupational exposure to HIV. A case-control study has demonstrated that PEP with zidovudine was associated with an 81% decrease in the odds of HIV transmission with a percutaneous exposure in the occupational setting. Although there is no data to show that ART is effective at preventing transmission from non-occupational exposures, the principles of managing patients with recent HIV exposure are similar whether the exposure occurs in an occupational or non-occupational setting. The data supporting ART NO-PEP is limited to animal studies and observational studies (with small sample sizes).

HIV EXPOSURE RISK ASSESSMENT

A detailed and careful history of the exposure event is the first step in evaluating a patient.

Exposure With Known HIV Positive Source	Estimated Risk of Transmission Per Exposure
Needle stick injury / Sharing needles and syringes	1/125
Receptive anal intercourse • Ejaculation • Withdrawal	 1/70 1/155
Receptive vaginal intercourse	1/1250
Insertive anal intercourse	1/900
Insertive vaginal intercourse	1/2500
Receptive fellatio with ejaculation	Not measurable
Sharing needles	1/125

Table 1. Estimated risks of HIV transmission per type of exposure

Table 1 lists the estimated risk of HIV transmission following a single percutaneous occupational, sexual, or injection drug exposure. Patients should be told that these are estimates, and in reality, the odds of infection with a specific exposure are also affected by other factors such as the viral load of the infected person, presence of other sexually transmitted infections, the size of the inoculum, and so forth.

If the source is of unknown HIV status, the risks will be reduced proportionately to the estimated HIV prevalence in the population from which the source comes, e.g. if the estimated prevalence of HIV infection in 10% in MSM population, the risk of transmission per exposure will be reduced 10 times.

INDICATIONS FOR PEP

The following criteria should be used:

- There is a risk of exposure to HIV (unprotected anal or vaginal intercourse, receptive fellatio with ejaculation) with: (1) a partner known to be HIV-infected, or (2) in at-risk group (MSM, sex workers, persons who inject drugs), or (3) sexual assault
- Patient must be counselled and make a commitment to adherence and follow-up
- Patient must make an informed decision regarding potential risks and benefits of PEP offered
- PEP should be started as soon as possible after exposure and within 72 hours to have optimum effect.

PEP is not routinely recommended for sexual exposure when an HIV-positive source has an undetectable viral load.

PEP is not recommended for oral sexual exposure, mucous membrane or non-intact skin exposure or needle-stick injury from discarded needle stick in the community.

TREATMENT

Recommended Regimen(s)

A 28-day course of PEP is recommended. No strong evidence exists, based on randomised clinical trials, that any specific combination of antiretroviral medication is optimal for PEP use. We have opted to follow the Australian guidelines for PEP that recommend 2-drugs for exposures with a source of unknown HIV status. For exposures with a source who is known to be HIV-infected but not on treatment, has unknown viral load or viral load that is not optimally suppressed, a 3-drugs combination is recommended. Reviews of 2-drugs versus 3-drugs for PEP have not showed inferiority to a 3-drug course.

Two-drug Regimen

1. Tenofovir disoproxil fumarate (TDF) 300mg *and* emtricitabine (FTC) 200mg orally daily

Three-drug Regimen

1. Tenofovir disoproxil fumarate (TDF) 300mg *and* emtricitabine (FTC) 200mg orally daily

   plus

   a. Dolutegravir (DTG) 50mg orally daily

   or

   b. Raltegravir (RTG) 400mg orally BD

   or

   c. Rilpivirine (RPV) 25mg orally daily

Note

- The recommended medications are generally well tolerated with few side effects.
- Tenofovir disoproxil fumarate (TDF): use with caution or avoid in renal disease (eGFR <60), dose reduction required in renal impairment.
- Dolutegravir (DTG): If taking products containing Mg, Al, Ca or Fe, to take 2 hours before or 6 hours after the dose.
- Rilpivirine (RPV): Must be taken with food. If taking H_2 blockers, antacids, to take 2 hours before or 4 hours after dose.

BASELINE TESTS AND FOLLOW-UP

- Rapid HIV 4th Gen test
- Evaluation of other STI, including HBV and HCV, where indicated
- Liver and renal function tests (except for 2-drug regimen)
- Patients should be reviewed after 4 weeks to document adherence and adverse effects and reinforce prevention messages.
- HIV testing should be performed at 1 and 3 months post-exposure.

KEY POINTS FOR PATIENT COUNSELLING

- PEP provides high level of protection, but is not 100% effective, as there have been documented cases of seroconversion despite PEP.
- Adherence to dosing and completion of PEP is crucial to optimise effect.
- Side effects may be encountered with the medications.
- Safer sex and how to prevent future exposures must be addressed.
- Persons who have had high-risk exposures that justified use of PEP should be evaluated for PrEP

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1. ASHM. Post-exposure prophylaxis after non-occupational and occupational exposure to HIV: Australian national guidelines: supporting the HIV, viral hepatitis and sexual health workforce. 2016;22.

2. Pierce et al. Comparing non-occupational post-exposure prophylaxis drug regimens for HIV: insights from a linked HIV surveillance system. Sexual Health, 2017, 14, 179-187

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HIV PRE-EXPOSURE PROPHYLAXIS (PrEP)

INTRODUCTION

Pre-exposure prophylaxis with co-formulated tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) is highly effective in reducing the chances of contracting HIV infection. The use of PrEP is now recommended in national guidelines in many countries including the United States, United Kingdom and Australia. The World Health Organization recommended in 2015 that "oral pre-exposure prophylaxis (PrEP) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches". In 2017, WHO also published an implementation tool to guide countries on the introduction and implementation of PrEP.

HIV transmission among men who have sex with men (MSM) has been rising in Singapore similar to most other countries, indicating the need for additional methods of HIV prevention, such as PrEP, especially among at risk populations. Mathematical modelling has shown that ART alone cannot reduce HIV incidence to very low levels. PrEP can be used cost-effectively in addition to ART to reduce incidence further.

EVIDENCE FOR EFFICACY

Men who have Sex with Men (MSM)

The Pre-exposure Prophylaxis Initiative (iPrEx) study was a double-blind, placebo-controlled, multi-centre RCT conducted among MSM and transgender (TG) females The TDF/FTC group was associated with a 44% reduction in the risk of HIV acquisition (95% CI, 15-63). Plasma and intracellular drug-levels showed there was a *92% reduction* in the risk of HIV acquisition (95% CI, 40-99) in persons with detectable levels of TDF/FTC versus those without.

The IPERGAY study was a double-blind, multi-centre RCT conducted among MSM, comparing on-demand TDF/FTC versus placebo. The on-demand regimen involved taking:

- 2 tablets of TDF/FTC 2 to 24 hours before sex, and
- 1 tablet a day during periods of sexual risk and for 48 hours (two doses) after sex.

The study demonstrated the efficacy of on-demand regimen when it showed that 14 people became infected with HIV in the placebo group compared with 2 in the TDF/FTC group, a *RRR of 86%* (95% CI 40-98%). This figure was even higher 97% in the open-label extension of the trial.

The PROUD study was a randomised, open-label trial that recruited MSM in England. Participants either receive daily TDF/FTC immediately or after a deferral period of 12 months. A total of 23 participants became infected with HIV over the course of the study; three in the daily TDF/FTC group and 20 in the deferred group. This represents a *RRR of 86%* (90% CI 64-96%), the number needed to treat to prevent one HIV infection over 1 year was 13 (90% CI 9—23%).

The DISCOVER study was an RCT conducted on MSM and TG women that studied co-formulated tenofovir alafenamide and emtricitabine (TAF/FTC). It demonstrated the non-inferiority of TAF/FTC when compared to TDF/FTC. TAF/FTC arm had fewer renal and bone density side-effects, although the clinical significance of these findings is as yet unknown. Its use in heterosexual men and women has not been reported, nor is it recommended for on-demand use.

Heterosexuals

The Partners PrEP trial was a double-blind RCT of daily TDF/FTC or TDF for the prevention of acquisition of HIV by the uninfected partner HIV-discordant heterosexual couples in Uganda and Kenya, conducted from 2008 to 2010. Compared to placebo, the overall efficacy estimates were 75% (95% CI 55-87; P<0.001) for TDF/FTC, and 67% (95% CI 44-81; P<0.001) for TDF alone. When plasma TDF levels were measured, for participants in the TDF/FTC group, detectable drug was associated with a *90% reduction* in the risk of HIV acquisition.

Injecting Drug Users

The Bangkok Tenofovir Study was a double-blind, placebo-controlled study on the efficacy of daily oral TDF among injection drug users. as 48.9% (95% CI, 9.6-72.2; p=0.01), however detectable levels of tenofovir in the blood was associated with *73.5% reduction* in the risk for HIV acquisition (95% CI, 16.6-94.0; p=0.03).

EVIDENCE FOR SAFETY

Renal Function

TDF has been associated with increased renal toxicity and osteoporosis when used as regular treatment for people living in HIV, but the same effect has not been seen in patients on PrEP. A metanalysis of 13 randomised trials comparing the use of TDF/FTC or TDF alone as PrEP versus placebo found no significant differences in risk of grade 3/4 clinical adverse events, bone or renal adverse outcomes. In cases where there was substantive decline (i.e. more than 25% of baseline) in the eGFR, cessation of PrEP resulted in normalization of the eGFR in almost all patients. A meta-analysis of global programme data found that <1% who were screened before starting oral PrEP had abnormal creatinine clearance levels and less than 3% of oral PrEP users experienced a decline in creatinine clearance to <60 mL/min. Individuals over 50 years, with baseline creatinine clearance of <90 mL/min and with kidney-related comorbidities such as diabetes or hypertension, had a higher probability of declining to abnormal levels of creatinine clearance. Less than 1% of oral PrEP users younger than 30 years' experience abnormal creatinine clearance. In view of the above data, the population of individuals who require creatinine monitoring and the frequency of creatinine monitoring has been changed to better adapt the above findings.

There is no data concerning the use of PrEP for individuals with eGFR <60ml/min. Hence, the use of TDF should still be stopped in individuals whose eGFR falls to <60ml/min. For MSM and TG women who have sex with men with eGFR between 30ml/min and 60ml/min, there is now an option to use TAF/FTC instead. As there is limited data on the use of TAF in patients with CrCl <30mL/min, most international guidelines have advised avoiding the use of TAF in these patients.

Bone Mineral Density

A sub-study of 500 participants in iPrEx who underwent DEXA scans showed at 24 weeks a small decrease in BMD (spine and total hip measures) of 0.7-1% in TDF/FTC group compared with placebo. In the US MSM Safety Trial, DEXA scans done for 184 men showed that TDF use was associated with small decrease in BMD (1% decrease at femoral neck, 0.8% decrease for total hip). TDF was however not associated with reported bone fractures at any site.

Hepatitis B Virus (HBV) Infection

Both TDF and FTC are active against HIV and HBV infections. All individuals who test positive for the hepatitis B surface antigen (HBsAg) will need a baseline HBV DNA quantitative assay to determine the level of replication prior to starting PrEP. HBV DNA levels should be monitored 6-12 monthly in these cases. These individuals should be started on daily PrEP rather than on demand PrEP. It is important to emphasize adherence to prevent reactivation of HBV infection with potential acute liver injury and to reduce the risk of developing TDF resistant HBV infection. If PrEP is no longer required, a decision will have to be made on whether TDF/TAF is needed for treatment of HBV infection. These individuals need to be monitored by an experienced clinician after stopping PrEP.

DRUG RESISTANCE

A meta-analysis looked at six trials that reported cases of TDF or FTC drug resistance using standardised genotypic laboratory assays. Among those acutely infected at enrolment, the risk of developing TDF or FTC mutations was significantly higher in the active groups compared with placebo group (risk ratio=3.34, 95% CI: 1.11-10.06, P=0.03).

However, among participants who seroconverted post-randomization, TDF or FTC resistant infections were uncommon, with insufficient power to calculate relative risks. There were a total of six (2%) TDF or FTC drug-resistant infections out of 533 cases of incident HIV infection post-randomisation across study arms including five FTC mutations among those randomised to PrEP and one mutation among those randomized to placebo.

COMPENSATORY SEXUAL BEHAVIOUR AND STI INCIDENCE

In the PROUD study, there was no difference in the total number of sexual partners at 1 year or in the frequency of bacterial STI. However, a greater proportion of the immediate group reported condomless receptive anal sex with 10+ partners at 1 year compared to the deferred group (21% vs 12%, p=0.03). In the IPERGAY open-label phase, reported condomless receptive anal sex during the most recent sexual intercourse increased from 77% at baseline to 86% at the 18-month follow-up visit (p=0.0004). The incidence of a first bacterial STI in the observational study (59.0 per 100 py) was not higher than that seen in the randomized trial (49.1 per 100 py) (p=0.11).

Some reports have shown an increase in condomless anal intercourse and bacterial STIs after PrEP initiation. On the other hand, some modelling exercises have predicted falls in STI rates after the implementation of a combination HIV/STI screening and prevention programme; real world evidence of this was seen in a report from a London clinic. These findings underline the importance of providing PrEP as part of a properly managed HIV/STI programme.

SUMMARY OF RECOMMENDATIONS FOR PREP PROVIDERS

The recommendations for the provision of PrEP are summarised below. These recommendations are based on the extant literature showing the efficacy and safety of PrEP, and reflect prevailing practice as set out in international and national guidelines in other settings.

Target Population

Key populations who have substantial risk of HIV infection:

- MSM
- Transgender persons
- Heterosexual men with multiple partners
- Sex workers/people who exchange sex for money
- Serodiscordant couples

People with the following sexual behaviours should also be considered for PrEP:

- Sex with a person with HIV who is not on suppressive ART or has a detectable viral load in last 6 months
- Vaginal or anal intercourse without consistent use of condoms with more than one partner in the last six months
- Bacterial STI in the last six months
- Received HIV PEP in the last six months
- Reported concerns about consistent use of condoms in the future e.g. has difficulties using condoms
- Use of recreational drugs during sex (“chemsex”) especially methamphetamines in the last 6 months (or indication that they may have such behaviour)
- Requesting for PrEP: on a case-by-case basis e.g. left a monogamous partnership and will likely be having unprotected sex in future

Contraindications to PrEP

- Known HIV infection
- Clinical symptoms suggestive of acute HIV infection / HIV seroconversion illness
- Known impairment of renal function (estimated eGFR <60ml/min)
- Allergy or other known contraindication to any of the drugs in the PrEP regimen

Patient Encounter for PrEP Providers

It is important to take history and document the following for any patient encounter about PrEP:

- Date of last unprotected sexual activity
- HIV and STI screens in the last year, specifically date of the last HIV test
- History of any bone, renal disease and hepatitis B infection

Counselling a patient for PrEP should include:

- PrEP does not confer protection against other STI or pregnancy
- Importance of HIV/STI screening every 3 months
- Importance of drug adherence, taking TDF/FTC
- Dosing regimen and pros and cons of daily and on-demand PrEP
- Risks and benefits of online purchases of generic drugs (Note: It is legal for a patient to obtain 3 months of generic drug via the internet for personal use)
- Risk reduction including condom negotiation, information and support with sex with recreational drugs (chemsex) as appropriate (Note: Regulation 19 of MDR: Treatment of Drug Addicts)

Types of PrEP Regimen

PrEP Regimen	Indicated Population	Notes
Daily PrEP Daily dosing of co-formulated TDF/FTC	MSM Heterosexual men and women Trans persons Sex workers	Needs to be taken for 7 days before high levels of protection are achieved for both vaginal and rectal exposure to HIV. Daily TAF/FTC can also be used by MSM and TG women.
On-Demand PrEP (Event-driven PrEP) A double dose (two tablets) of co-formulated TDF/FTC to be taken **2-24 hours before** potential sexual exposure, to be followed by **single doses 24 and 48 hours after** the initial dose	MSM only	In heterosexual persons, on-demand PrEP has not been investigated. Based on pharmacokinetic concerns, we do not recommend event-driven PrEP for this population. In the absence of other data, transpersons should also not be offered event-driven PrEP

Types of PrEP Regimen

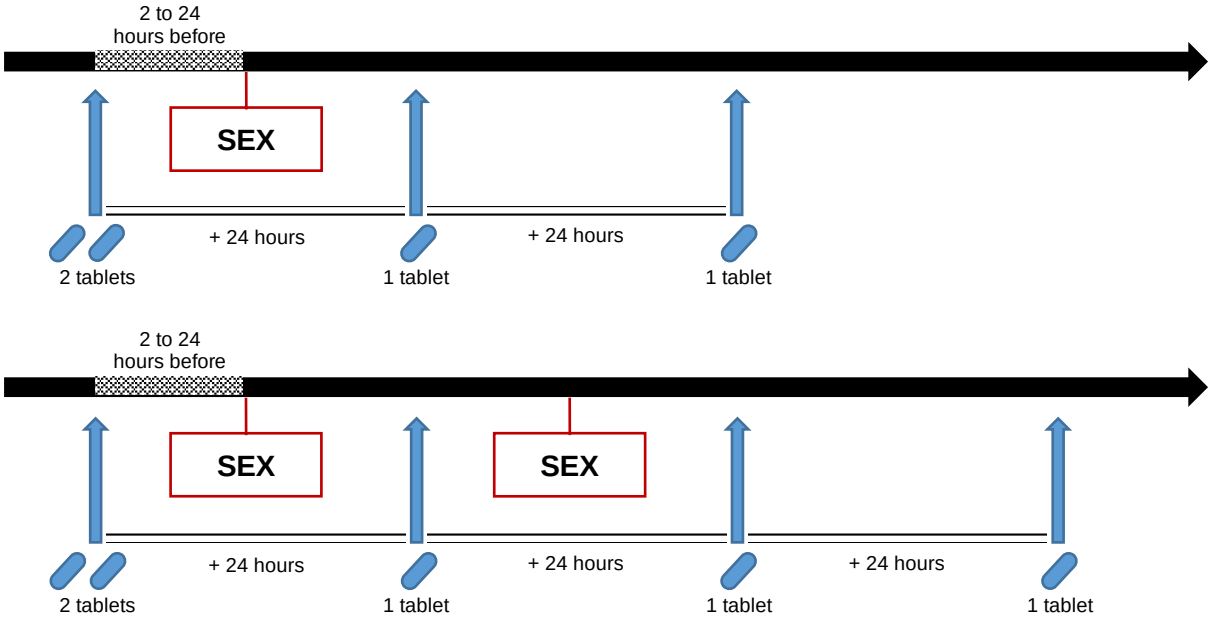

Figure 1 - Event-Driven PrEP

First Consultation

Ensure that patient is HIV-negative	Use 4th generation HIV test (either conventional HIV EIA or rapid POCT blood test) However, if there was recent high-risk exposure, it is advisable not to rely on a POCT as these are less sensitive that conventional EIA If last high-risk exposure in the last 4 weeks ago, repeat HIV test after 4 weeks	Persons who present signs or symptoms consistent with acute HIV infection should not be commenced on PrEP until HIV infection has been excluded. For individuals at high imminent risk of HIV infection it is preferable to start PrEP promptly after confirming that a POCT is negative and that there is no clinical suspicion of acute HIV infection
	If last high-risk exposure was within the last 72 hours, consider PEP	See *Post-exposure prophylaxis guidelines*
Baseline Renal Function Testing	Serum creatinine	Estimated creatinine clearance rate using the modified Cockcroft-Gault equation
	Urinalysis for proteinuria	Only for patients with pre-existing risks for renal impairment, e.g. diabetes, hypertension
HBV Screening	Hep B surface antigen (HBsAg) and antibody (anti-HBs)	HBV vaccination should be offered in non-immune persons If patients test positive for hepatitis B, they should be referred for further evaluation and not be offered on-demand PrEP.
HCV Screening	Hep C antibody (anti-HCV)	Referral for Hepatitis C treatment if positive
Sexually Transmitted Infection (STI) Screening	Syphilis screening	
	Gonorrhoea, chlamydia	At relevant sites (urethral, rectal, pharyngeal)
Pregnancy Screening	Urinary beta-HCG	Contraception should be discussed and provided for women who are on PrEP and who do not wish to become pregnant
Prescribe PrEP	Prescription should not exceed 3 months or 90 days with no automatic refills	For patients obtaining medications from external sources, a printed, signed and dated prescription should be provided
Counselling PrEP should be offered as part of a comprehensive HIV/STI prevention package	Effectiveness of PrEP	PrEP is highly effective if taken as prescribed as part of an overall HIV/STI prevention strategy
	Adherence	It is important to take PrEP every day (for daily PrEP) and according to the schedule (for on-demand PrEP) for it to be effective
	Regular HIV/STI tests	It is important to return for visits to get tested for HIV/STI, assess side-effects, and obtain new prescription so that PrEP is not interrupted
	Condom use	PrEP does not prevent other STIs, reinforce condom use. PrEP also does not prevent pregnancy, contraception should be used to prevent pregnancy if needed

4 Weeks After Commencing PrEP

Opportunity to review adherence, adverse events and HIV/STI window periods	Repeat HIV testing: use 4th generation HIV test (either routine HIV EIA or rapid POCT)	If there are concerns about adherence to PrEP in the first 4 weeks, or if there was a recent high-risk exposure more than 3 days prior to PrEP initiation
	Check adherence	Confirm that daily / on-demand regimens are being taken correctly. Document periods of stopping and reasons
	Check condom use	
	Check for side-effects	

Subsequent Clinic Visits

Frequency of visits	Every 3 month (up to 6 month if person is reliable e.g. uses condoms regularly and has very few sexual partners)	
Ensure that patient remains HIV-negative	Use 4th generation HIV test (routine HIV EIA is preferred over rapid POCT) Test results from anonymous test sites or HIV self-tests are not acceptable.	There is growing evidence that PrEP or early ART initiation in acute infection can cause blunting of the HIV-1 antibody response, with both non-reactive or atypical and non-progressive HIV serology.
PrEP review	Check adherence	Confirm that daily / on-demand regimens are being taken correctly. Document periods of stopping and reasons
	Check condom use	
	Check for side-effects	
Renal function monitoring	Serum creatinine - 6 monthly All individuals should have a repeat creatinine 1-3 months after starting PrEP.	In those younger than 50 years of age without any co-morbidities, no further creatinine monitoring is required if the repeat creatinine test is normal. Those with kidney related co-morbidities or age 50 years and above should have serum creatinine checked at least once every 12 months.
	Urinalysis for proteinuria - 6 monthly	Only for patients with pre-existing risks for renal impairment, e.g. diabetes, hypertension
STI Screening and Treatment	Syphilis, gonorrhoea, chlamydia screening - 3 to 6 monthly	Frequency of screening depends on patient-reported sexual risk behaviour
Hepatitis C Screening	Anti-HCV - 12 monthly	For MSM and transgender women
Pregnancy Screening	Urinary beta-HCG - 3 monthly	
Prescribing PrEP	Prescription should not exceed 3 months, or 90 days with no automatic refills	For patients obtaining medications from external sources, a printed and endorsed prescription should be provided
Other Services	Vaccination against Hepatitis A, B and HPV as appropriate	
	Contraception for women on PrEP who do not wish to become pregnant	
Counselling	Adherence	Key Messages as outlined above
	Regular HIV/STI tests	
	Condom use	
Stopping PrEP	The need for continued PrEP should be determined based on assessment of the patient's risk of HIV infection	Patients should continue daily PrEP for 2 days after anal sex and for 7 days after vaginal sex
Linkage to care for patients who seroconvert	All patients who test positive for HIV should be referred for treatment	HIV-infected patients can be started on HIV treatment without interruption

Cessation of PrEP

Assess HIV serostatus	Use 4th generation HIV test (either routine HIV EIA or rapid POCT)	
Hepatitis B considerations	Patients who are HBsAg-positive and stop PrEP should have their liver function and hepatitis B viral load monitored after cessation of PrEP as there is a risk of reactivation of infection	They should be evaluated by a clinician experienced in the management of HBV infection to ascertain their need for ongoing HBV treatment, and to monitor for any hepatic flares that occur if PrEP is ceased
Counselling	Advice on restarting PrEP Any person who wishes to restart taking PrEP should repeat the baseline evaluations. Previous discontinuation of PrEP for any reason (except seroconversion to HIV) should not exclude the person from restarting PrEP	Patients should be counselled that they should consider re-initiation of PrEP if there is renewed risk of HIV infection, e.g. • Entering a period of engaging in unprotected sex • Leaving a long-term relationship • Starting a serodiscordant relationship with a partner who is yet to be virally suppressed, or with a partner of unknown HIV serostatus • Other risk factors for HIV acquisition

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HUMAN IMMUNODEFICIENCY VIRUS (HIV)

DEFINITION

The HIV/AIDS pandemic was the major infectious disease of the last century and remains one of the most serious health challenges in the 21st century. It disproportionately affects resource-poor countries and key affected populations viz. men who have sex with men (MSM), sex workers and their clients, and people who inject drugs. An estimated 37.7 million people were living with HIV in 2020, 36.3 million people have died from AIDS-related illnesses since the start of the epidemic. There were 1.5 million new HIV infections globally in 2020.

Of particular concern in Singapore is the increasing incidence and prevalence among MSM and the continuing high number of late-presenters.

CAUSATIVE ORGANISM

AIDS is caused by HIV-1, much less commonly by HIV-2. HIV-1 and 2 are enveloped, single-stranded RNA *Lentivirus* within the family *Retroviridae*. HIV-1 comprises four distinct lineages, M, N, O, and P, Group M is responsible for 99% of the pandemic form of HIV-1; groups N, O and P are restricted to West Africa. HIV-2 is also largely restricted to West Africa, where its overall prevalence is declining and being replaced by HIV-1. HIV has substantial genetic variability due to the error-prone function of its reverse transcriptase as well as the very rapid turnover of the virus in infected individuals. HIV-1 infection involves the interaction between the viral envelope protein gp120/41 and the CD4 molecule followed by a second interaction with a chemokine receptor, usually CCR5 or CXCR4. These receptors are found on activated CD4 T lymphocytes, monocyte-macrophages and dendritic cells. CCR5 is the predominant fusion cofactor in most transmitted HIV infections. The RNA genome is transcribed by a reverse transcriptase enzyme that produces a DNA copy of the HIV RNA. The viral DNA copy is spliced into the host DNA through the action of an integrase enzyme. Transcription of viral DNA into RNA yields genomic material of new viral particles or is translated into viral proteins. Cleavage of the latter into structural components of the virus is accomplished by proteases.

HIV TESTS FOR SCREENING AND DIAGNOSIS

HIV infection and AIDS are notifiable conditions. HIV testing should be voluntary, and individuals must not be tested without their knowledge, with the exception of anonymized sentinel surveillance when identifying information is removed and at government approved anonymous testing sites. Confidentiality of the result must be observed, and failure to do so may result in prosecution.

HIV testing is specifically recommended for the following persons:

- persons who seek evaluation and treatment for STIs
- individuals with signs and symptoms suggestive of HIV-related illnesses
- individuals whose behaviour puts them at risk for HIV infection
- pregnant women
- donors of blood, semen, and organs
- health care workers who perform exposure-prone invasive procedures

Post-test Counselling: Negative test

- Reinforce information on safer sex practices to reduce the risk of acquiring HIV.
- The significance of “the window period” and the necessity and timing of a repeat test should be discussed with the patient.

Post-test Counselling: Positive test

- We should expect persons to be distressed when first informed of a positive HIV test result.
- Persons who test positive for HIV should be counselled on behavioural, psychosocial, and medical implications of HIV infection. Refer to the Health Advisor.
- Linkage-to-care should be provided urgently, and referrals can be made to HIV/ID departments in NCID, NUH, SGH, other hospitals or private specialists.
- AIDS helpline numbers should be given for any future needs (Tel: 6295 2944)

HIV tests can be classified into conventional and rapid (see Tables 1 and 2). Conventional tests are those in which blood is collected and then sent to the laboratory for testing. Results from conventional tests are typically available from a few hours to a few days. Rapid point-of-care tests (POCT) tests can be done directly at the and yield results in 15 to 20 minutes. HIV tests are very accurate, but no test

can detect the virus immediately after infection. How soon after infection a test can detect infection depends upon different factors, including the type of test being used.

- *Antigen/antibody tests (4th generation EIA)* look for both HIV antibodies and p24 antigen. Tests that detect both antigen and antibodies are recommended for testing done in laboratories. There are also a rapid antigen/antibody test available.
- *Antibody tests (3rd generation EIA)* detect the presence of antibodies. There are no longer used.
- *Nucleic Acid Tests (NATs)* look for the actual virus in the blood. This test is expensive and is not routinely used for HIV screening unless the person recently had a high-risk exposure and needs an urgent result, or in cases with indeterminate Western Blot (WB) test results.

The initial HIV test is usually either a laboratory-based antigen/antibody test or a rapid test POCT. If this is positive, the person will be sent for follow-up testing. A positive initial laboratory based test is repeated on the same blood sample. Since 1989, repeatedly reactive specimens on immunoassays were then tested with a more specific HIV WB antibody test to confirm those results.

The WB has been the confirmatory test used in Singapore. A positive WB is defined by the detection of antibodies to all of the 3 main groups of HIV proteins: envelope (gp160, gp120 or gp41), gag (p24) and polymerase (p66 or p51). An indeterminate WB assay is commonly caused by the presence of unrelated antibodies that are cross-reactive with HIV proteins. It is possible that an indeterminate result is due to early HIV infection and incomplete evolution of the anti-HIV immune response. An indeterminate test result should be repeated at 1, 2 and 3 months to exclude an evolving HIV infection. A qualitative HIV RNA/DNA test can also be used to resolve an indeterminate HIV WB result.

In 2014, the US CDC proposed guidelines to improve the diagnosis of early HIV infection, infections by HIV-2, and reduce false negative and indeterminate results. This testing algorithm employs a 4th generation immunoassay. Reactive tests are tested with an immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies.

<u>Window Period</u>

The window period is the time between when a person gets HIV and when a test can accurately detect it. It varies from person to person and is also dependent on the type of HIV test. A negative test should be repeated 1 and 3 months after the last high-risk exposure for confirmation (see Figure 1).

- *3rd Generation EIA*: From 22 days
- *4th Generation EIA*: From 15 days
- *Western Blot*: From 6 to 12 weeks
- *Rapid antibody (3rd Gen) tests*: From 4 to 6 weeks after infection, most people will have enough antibodies to test positive. At 12 weeks after infection, about 98% of people will have enough antibodies to test positive.
- *Rapid antibody/antigen (4th Gen)* combination test: p24 antigen can be detected between 12 to 26 days after infection, antibodies can be detected between 20-45 days after infection
- *Rapid OraQuick by OraSure*: 3 months.

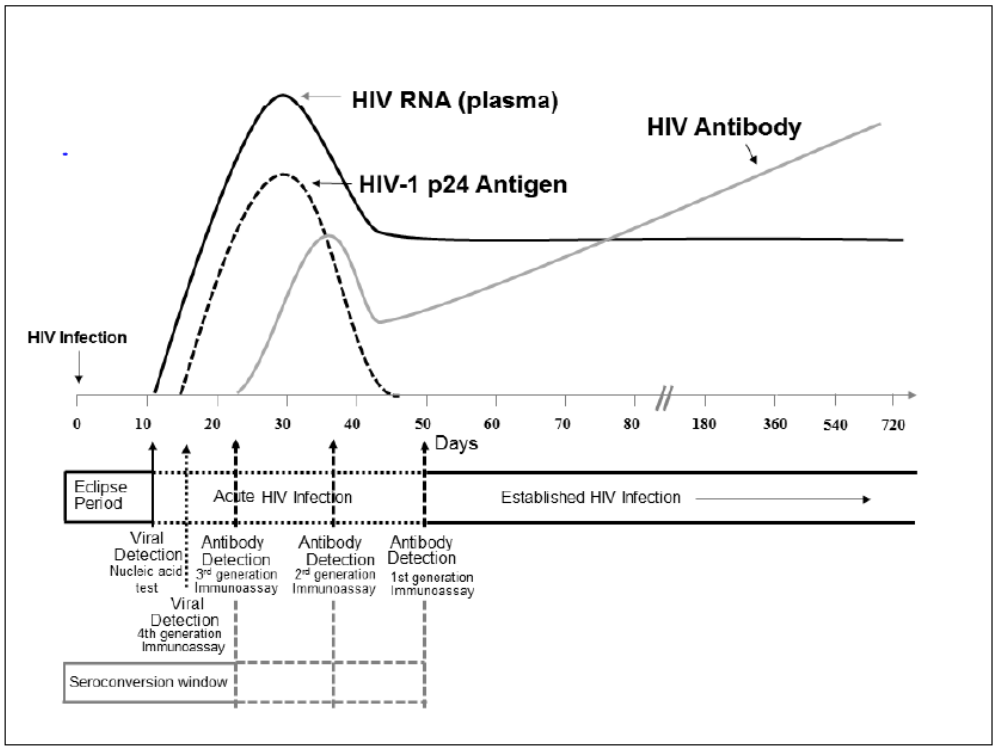

Figure 1 - Sequence of appearance of laboratory markers for HIV-1 infection
(Reference: Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. Available at http://stacks.cdc.gov/view/cdc/23447. Published June 27, 2014.)

Anonymous HIV Counselling and Testing Service

- The first ATS was started in 1991 and is operated by Action for AIDS on Tuesday and Wednesday evenings from 6.30 pm to 8 pm and Saturdays from 1 to 4 pm, at the DSC Clinic, 31 Kelantan Lane, Singapore 200031. Check https://afa.org.sg for open date schedules.
- Please refer to https://www.healthhub.sg/a-z/diseases-and-conditions/18/topics_hiv_aids for listing of other clinics that offer ATS.

Tests	Specimen Type	Sensitivity for established HIV infection	Specificity	"Window Period"	Time to perform test and receive results	Able to detect HIV2
HIV RNA / DNA Qualitative Assay (NAT)	Plasma	Lower than immunoassays by 2 to 4%	99.6 to 99.9%	10 days	4 hours to perform	No
HIV RNA Quantitative (viral load) Assay (NAT)	Plasma	Limit of detection varies	99.4 to 100%	10 days	1-2 days to perform, depends on test kit	No
HIV EIA 3rd Generation (Antibodies)	Serum or Plasma	99.80% to 100%	99.13 to 100%	22 days	~ 4 hours to perform test	Yes
HIV EIA 4th Generation (Antigen & Antibodies)	Serum or Plasma	99.76% to 100%	99.50 to 100%	15 days	~ 4 hours to perform test	Yes
HIV Western Blot (WB) (Antibodies)	Serum or Plasma	97.5% to 100%	99.9 to 100%	6 to 12 weeks Indeterminate may indicate early HIV infection	1-2 days depending on kit	No FDA-approved HIV-2 WB; Laboratory-validated HIV-2 WB available at some labs.

Table 1 - Characteristics of Conventional HIV Tests

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Rapid Test Kit	Description	Specimen Type	HIV 1/2 Differentiation	Sensitivity For Established Infection	Specificity
Alere Determine HIV-1/2 Test Kit	Detection of antibodies to HIV-1 and HIV-2	Serum, Plasma, Whole Blood via Venepuncture or Fingerstick	No	100%	99.75%
Alere HIV Combo	Detection of Ab to HIV-1 and HIV-2 and HIV-1 p24 Ag. Reactivity on Ab bar alone, Ag bar alone or both, is considered a reactive result.	Serum, Plasma, Whole Blood via Venepuncture or Fingerstick	No	100%	99.72% based on combined Ag and Ab,99.96% if based on Ab only, 99.72% if based on HIV p24 Ag only
Bio-Rad Genie Fast HIV 1/2	Detection of Ab to HIV-1 and HIV-2.	Serum, Plasma, Whole Blood via Venepuncture or Fingerstick	No	100%	99.5%
Cell ID Smart HIV 1/2 Rapid Diagnostic Test	Detection of Ab to HIV-1 and HIV-2.	Serum, Plasma, Whole Blood (Capillary)	No	100%	100%
MP Diagnostics MULTISURE HIV Rapid Test	Detection and differentiation of Ab to HIV-1 and HIV-2.	Serum, Plasma, Whole Blood (Capillary)	Yes	100% HIV-1 differentiation: 97.55%, HIV-2 differentiation: 93.94%	99.12%
Standard Diagnostics SD BIOLINE HIV 1/2 3.0	Detection of Ab to all isotypes (IgG, IgM and IgA) specific to HIV-1 including subtypes-O and HIV-2.	Serum, Plasma, Whole Blood via Venepuncture or Fingerstick	Yes	100%	99.8%
Orasure OraQuick Rapid HIV-1 /2 Antibody Test	Detection of Ab to HIV-1 and HIV-2	Serum, Plasma, Whole Blood via Venepuncture or Fingerstick, Oral fluid,	No	99.3% for oral fluid, 99.6% for plasma, 99.6% for Whole Blood (Fingerstick), 100% for HIV-2 serum & plasma samples 100% for HIV-2 Whole Blood (Fingerstick) and Oral Fluid	99.8% for oral fluid, 99.9% for plasma, 100% for Whole Blood (Fingerstick),

Table 2 - Characteristics of Rapid HIV Test Kits

CLINICAL FEATURES

Different classifications of HIV infection exist, depending on the purpose and geographical application. HIV infection often manifests as an acute infection that is followed by an asymptomatic period that can last for several years.

Acute or Primary HIV Infection

This presents as an acute febrile illness 2 to 4 weeks post-infection, and may be accompanied with lymphadenopathy, pharyngitis, maculopapular rash, orogenital ulcers and meningoencephalitis. Profound transient lymphopenia (including low CD4) can develop, and opportunistic infections may occur. These infections should not be confused with clinical staging events developing in established HIV infection. Primary HIV infection can be identified by recent appearance of HIV antibody or by identifying viral elements (RNA or DNA. or p24 antigen) with negative (or weakly reactive) HIV antibody. The level of HIV in the blood is very high, which greatly increases the risk of HIV transmission.

Untreated HIV-infected persons may develop a variety of infective conditions that arise from progressive depletion of CD4 T cells, that are killed by direct infection, bystander effects of syncytia formation, chronic immune activation, lymphoid tissue damage and senescence. HIV infection is also characterized by marked chronic immune activation related to low-grade HIV replication, immune responses to HIV and to reactivated infections, loss of mucosal integrity with consequent microbial translocation, and increased production of pro-inflammatory molecules. Markers of inflammation in HIV-infected persons have been significantly associated with mortality, cancer, cardiovascular, neurological and liver disease.

Acquired Immunodeficiency Syndrome (AIDS)

AIDS is the final, most severe stage of HIV infection. US CDC defines a person infected with HIV has AIDS if he/she presents with either a CD4+ T-cell count <200 cells/µl (or a CD4+ T-cell percentage of total lymphocytes <14%), or *opportunistic infections and malignancies* that include:

- Cervical cancer (invasive)
- Cryptococcosis (extrapulmonary)
- Cryptosporidiosis (chronic intestinal for longer than 1 month)
- Cytomegalovirus disease (other than liver, spleen or lymph nodes)
- Encephalopathy (HIV-related)
- Herpes simplex (chronic ulcers for more than 1 month or bronchitis, pneumonitis or esophagitis)
- Histoplasmosis (disseminated or extrapulmonary)
- Kaposi's sarcoma
- *Mycobacterium avium complex*
- *Mycobacterium* other species (disseminated or extrapulmonary)
- *Pneumocystis jiroveci* pneumonia
- Progressive multifocal leukoencephalopathy
- Toxoplasmosis of the brain
- Tuberculosis

TREATMENT

The following laboratory tests performed during initial patient visits can be used to stage HIV disease and to assist in the selection of antiretroviral (ARV) drug regimens:

- CD4 T-cell count
- Plasma HIV RNA (viral load)
- FBC, LFT, renal function tests, thyroid function tests
- Urinalysis
- Serology for hepatitis A, B, and C viruses
- Syphilis serology
- Toxoplasma and CMV antibody tests
- Fasting blood glucose and serum lipids
- Chest XR
- Genotypic resistance testing
- Serum cryptococcal antigen
- T-SPOT TB or Quantiferon-TB Gold

Newly diagnosed HIV-infected persons should receive psychosocial evaluation including ascertainment of behavioural factors indicating risk for transmitting HIV. They may require referrals for specific

behavioural intervention (e.g. substance abuse), mental health disorders (e.g. depression), or emotional distress. They might require assistance with securing and maintaining employment and housing as well as medical insurance status and adequacy of coverage. Women should be counselled or appropriately referred regarding reproductive choices and contraceptive options.

The goals of treatment are to maximally and durably suppress plasma HIV RNA, to restore and preserve immunologic function, to reduce HIV-associated morbidity, to prolong the duration and quality of survival and to prevent HIV transmission. ARV therapy (ART) is recommended for all individuals with HIV, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection. ART in individuals with HIV also prevents HIV transmission. When initiating ART, it is important to educate patients regarding the benefits and considerations of ART, and to address strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as possible.

Present-day ART regimens are very effective, have a lower pill burden and tolerability, and improved dosing convenience compared with previous regimens. There are over 25 licensed drugs that block HIV replication at many steps in the virus lifecycle available. There are also several fixed dose single-tablet regimens of ARV for added convenience. ARV medications are fundable under Medisave, Medifund and MAF schemes for selected patients and are on standard drug list in government hospitals. These schemes together with availability of generic versions of many ARV has made treatment affordable for most patients. An ARV regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (booster). Current evidence favours INSTI as the 3rd ARV drug on the basis of efficacy.

Initial ARV regimens achieve and maintain similar virologic suppression rates in nearly all patients. Clinicians and patients have many options and may select a regimen based on considerations in addition to antiviral potency. Considerations include short- and long-term adverse effects, ease of administration, drug interactions, risk of resistance if virologic failure occurs, and cost. Subsequent ART regimen switches for virological failure are guided by the results of resistance testing.

For low-income and middle-income countries, WHO also recommends ARV therapy should be initiated in all adults and adolescents living with HIV, regardless of clinical stage and at any CD4 cell count for treatment and prevention of transmission. Its recommended first-line ARV regimens for adults consist of two NRTIs plus a INSTI.

PREVENTION

Condoms are highly effective for preventing HIV transmission via anal and vaginal sex. For a risk exposure assessment, refer to chapters on PEP and PrEP.

PARTNER NOTIFICATION

HIV-infected patients should be encouraged to notify their partners and to refer them for counselling and testing. This can be assisted by Medical Social Workers (MSWs) and counsellors.

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HUMAN PAPILLOMAVIRUS (HPV)

DEFINITION

Papillomaviruses are a group of small DNA viruses that have been detected in a large number of vertebrates; they induce epithelial cell proliferation and infections that are highly species-specific.

Anogenital warts are benign lesions caused by human papillomavirus (HPV). 90% are caused by non-oncogenic HPV types 6 or 11. HPV types 16, 18, 31, 33, and 35 can also be found in anogenital warts but may be associated with high grade squamous intraepithelial lesions (HSIL) in the cervix, vulva, vagina, penis, anus and oropharynx.

HPV infection is very common and most infections do not result in clinically visible genital tract lesions. Incubation period varies between 3 weeks to 8 months. Most infections resolve spontaneously within a year.

CLINICAL FEATURES

HPV infection occurs as:

1. Clinical lesions: condylomata acuminata, papular and flat warts
    - condyloma acuminata: exophytic, filiform, cauliflower-shaped warts, HPV types 6 and 11 in >90% of cases
    - multifocal: usually 5 to 15, in areas of trauma during sex, 1-10 mm diameter, may coalesce especially in immunosuppressed and in the presence of diabetes mellitus
    - may be coinfected with oncogenic “high-risk” HPV e.g. types 16 and 18
    - oncogenic HPV: mostly give rise to subclinical lesions, intraepithelial neoplasia (IN) and anogenital cancer
2. Subclinical lesions: only visible after application of acetic acid and magnification
3. Latent HPV infection defined when HPV DNA can be demonstrated in absence of clinical or histological evidence of infection.

LABORATORY TESTS

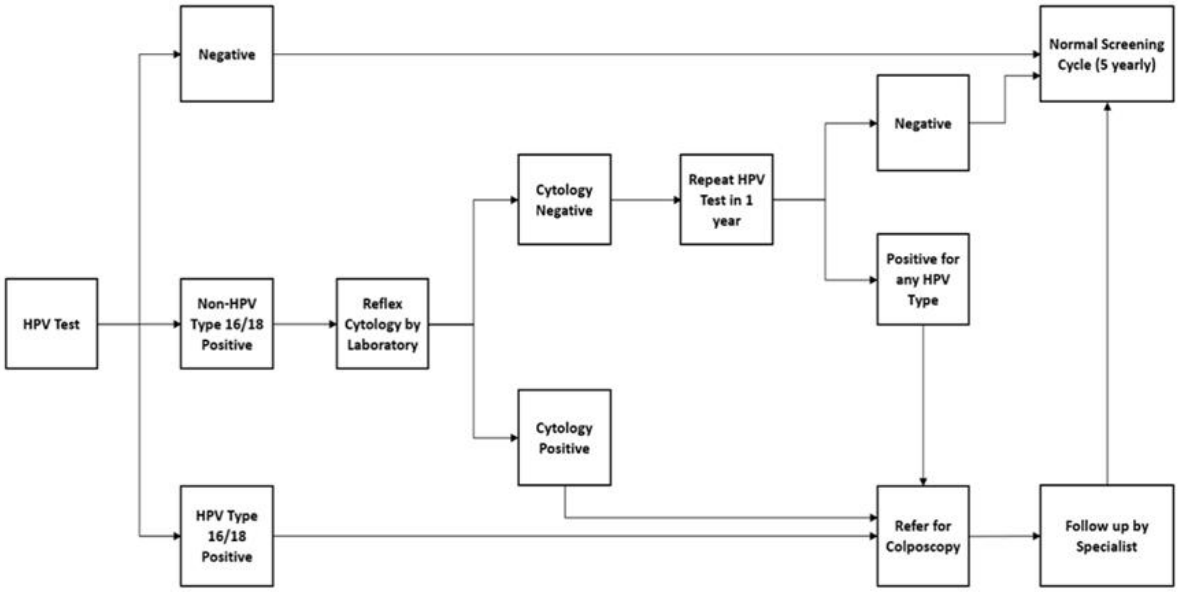
A clinical diagnosis is made from recognition of characteristic lesions.

1. Subclinical mucosal warts can be identified by turning white (acetowhite) after application of 5% acetic acid for 3 minutes. This can be applied onto discrete as well as suspected sub-clinical lesions; the mechanism for this aceto-whitening effect is not clear. One hypothesis is that acetic acid causes a reversible coagulation of some epithelial and stromal proteins. Note that this whitening effect may also occur in areas of abrasions or non-specific inflammation, and may also be seen in other infections such as candidiasis, and thus is not specific for HPV infection.

2. Skin biopsy is indicated for atypical cases, cases where the benign nature of papular or macular lesions is unclear. Features which may raise suspicion include pigmentation, depigmentation, pruritus, immune-deficiency and prior history of intraepithelial neoplasia. Biopsy may also be indicated when the lesions do not respond to standard therapy, or worsen during therapy.

3. If a clinical diagnosis has been made, HPV testing is not recommended to confirm anogenital wart diagnosis.

4. Screening for HPV in females according to national guidelines (2019), *see next page*:



TREATMENT

Anogenital warts display marked variability in their response to any mode of therapy; no treatment modality is completely satisfactory in eliminating HPV. The goal of treatment is to remove visible exophytic warts, not the eradication of HPV.

It is important to perform meatoscopy for meatal warts, proctoscopy for anal warts, and speculum examination with cervical cytology/colposcopy for female genital warts.

Recommended Regimen(s)

Penile, Vulval and Perianal Warts

Home therapy

1. Imiquimod (5% cream) **[Ib, A]**
    - 3x a week at bedtime, washed-off next morning.
    - Imiquimod is an immune response modifier that induces a cytokine response, including the production of interferon-α, tumour necrosis factor-α, as well as interleukins 1, 6, and 8, when applied to skin infected with HPV. In animal models imiquimod has demonstrated antiviral, anti-tumour, and adjuvant activity. Useful for thin lesions.
    - Duration: until clearance or 16 weeks maximum.
    - Therapeutic response may be delayed / slower than other modalities (mean 7-8 weeks).
    - Clearance in 56%: women 77%, men 40% (better results in uncircumcised men).
    - Clinical trials show an encouragingly low recurrence rate: 10-15%.
    - S/E erythema, burning, erosions after 3-4 weeks.
    - Not approved for use in pregnant women or internally.

2. Podophyllin 0.25% or 0.5% in ethanol **[Ib, A]**
    - Applied BD x 3 days, rest 4 days and repeat cycle.
    - Effective and inexpensive.
    - Not to be used in pregnancy or internally.

3. 5-Fluorouracil (5% cream)
    - Applied 1-3 times weekly x several weeks.
    - Use limited by high frequency and severity of local reactions (may appear 2-3 days later).
    - Possible use on intrameatal and intravaginal warts, and as an adjunct to laser therapy **[II, B]**.
    - For urethral warts: apply after each micturition.
    - Potentially teratogenic; advise contraception and avoidance in pregnancy.
    - Presently not approved by US FDA as a treatment for warts (off-label indication).
    - Not recommended for routine management.

4. Podophyllotoxin (0.15% cream) **[Ib, A]** (not easily available)
    - BD x 3 days a week, rest 4-7 days.
    - purified non-mutagenic extract of podophyllum plant.
    - binds to cell microtubules, inhibits mitosis, induces necrosis, maximal 3-5 days after application.
    - 60-80% clear after 1- 4 courses, less successful for circumcised men.
    - Recurrence rate ranges from 7-38%
    - S/E: transient burning, erythema, tenderness, erosions, usually after first course only, starting on day 3.
    - Contraindicated in pregnancy; women of childbearing age must use contraception
    - It is recommended that the physician or nurse applies the first treatment to demonstrate the proper technique of application and to identify the warts to be treated.

5. Cathechin 10/15% ointment (not easily available)
    - Applied TDS using finger to ensure coverage of warts with thin layer of ointment
    - Should not be washed off after use
    - Duration: until clearance of wart or 16 weeks maximum.
    - S/E erythema, pruritus/ burning, pain, ulceration, oedema, induration, vesicular rash.

Office Therapy

1. Cryotherapy: Liquid nitrogen **[Ib, A]**
    - Epidermal and dermal necrosis, thrombosis of vessels.
    - Weekly to fortnightly intervals, freeze-thaw-freeze cycle (-196 °C).
    - Open application by spray or cotton swab.
    - Simple, relatively inexpensive.
    - Safe during pregnancy.
    - S/E oedema, blister formation, scarring, pigmentary changes.
    - Initial response rate 63-89%.

2. Electrosurgery **[Ib, A]** with mask and smoke evacuator
    - Removal of warts under LA particularly useful for pedunculated warts, and small amounts of keratinized ones at anatomically accessible sites.

3. CO2 laser (10600nm) **[IIa, B]** with mask and smoke evacuator
    - Heats water to 100°C, evaporation of the cell, steam formation.
    - Effective, precise, minimal tissue damage, good healing.
    - Preferred treatment for lesions on the cervix and vagina.
    - Expensive, healing 2-4 weeks.

4. Scissor or scalpel excision **[Ib, A]**
    - Separation and elevation of lesions facilitates accurate removal, sparing of uninvolved skin.
    - Adrenaline contraindicated on penis and clitoris
    - Haemostasis can be achieved with an electrosurgery unit
    - Usually eliminates warts at a single visit, recurrence 20-30%

5. Trichloroacetic acid (50%-80%) **[Ib, A]**
    - Caustic agent: causes cellular necrosis.
    - For acuminate warts: anal, meatal, vaginal.
    - Applied at weekly intervals.
    - Safe during pregnancy.
    - A small amount of the chemical is applied to the warts, taking care to avoid contact with clinically normal skin.
    - As the product is allowed to dry, a white “frosting” develops.
    - Application of TCA usually causes several minutes of mild to moderate discomfort at the site.
    - Excessive amounts of unreacted acid should be washed off with liquid soap.
    - Acid can be prevented from causing further damage if the entire treated area is quickly dusted with talc or sodium bicarbonate.
    - Not effective for keratinized warts, not for large lesions, multiple sessions are not well tolerated.
    - S/E: burning sensation for up to 10 minutes after application, ulceration and scarring (rare).
    - Initial response rate: 70-81%, recurrence rate: 36%.

Vaginal Warts
- Cryotherapy, CO_2 laser, Electrosurgery or Trichloroacetic acid (TCA).

Cervical Warts
- Dysplasia must be excluded before starting treatment; cervical cytology and colposcopy (if necessary) are advised.
- CO_2 laser, Electrocautery or Cryotherapy.
- Podophyllin and podophyllotoxin are not recommended for treating cervical warts.

Meatal Warts
- Cryotherapy, Electrocautery, Podophyllotoxin 0.5%, Podophyllin 0.25% in ethanol, or 5-Fluorouracil 5% cream.
- Refer to urologist for management in refractory or extensive cases which extend beyond the meatoscope.

Anal Canal Warts
- Cryotherapy, Electrocautery, Surgical excision, or TCA.

CONSIDERATIONS IN PREGNANCY
- Imiquimod, podophyllin and podophyllotoxin should not be used in pregnancy.
- Genital warts should be removed in pregnancy because they can proliferate and become friable.
- There is also a risk (1 in 400) of transmission to the infant leading to laryngeal papillomatosis.

CONSIDERATIONS IN IMMUNOSUPPRESSED
- Immunosuppressed patients with warts do not respond as well to treatment, and may have more frequent recurrences after treatment. Squamous cell carcinomas arising in warts may occur more frequently, requiring biopsy for confirmation of diagnosis.

HPV VACCINATION
Currently HPV vaccines are not licensed for the treatment of existing HPV infection, or HPV-related diseases. Please refer to the chapter on Vaccinations for HPV vaccination.

FOLLOW-UP

- Provide clear information: causes, treatment, outcomes, and possible complications.
- Reassure: complete clearance will occur sooner or later.
- Advise smoking cessation for recalcitrant warts.
- Regular cervical cytology (PAP smears) for females.
- Condoms: with new partners till clearance is achieved; regular partner already exposed.
- Long latency periods mean that only one partner in a relationship may manifest warts.
- Current partners and recent (6 month) partners should be assessed for HPV and other STI.

MANAGEMENT OF SEXUAL CONTACTS

Patients should inform current partners about having genital warts because the types of HPV that cause warts can also be passed on to partners.

Partners should be counselled that they might already have HPV despite no visible signs of warts; therefore, HPV testing of sex partners of persons with genital warts is not recommended.

Partners might benefit from a physical examination to detect genital warts and tests for other STIs.

No recommendations can be made regarding informing future sex partners about a diagnosis of genital warts because the duration of viral persistence after warts have resolved is unknown.

References:

1. BASHH. (2015). United Kingdom National Guideline on the Management of Anogenital Warts

2. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

LYMPHOGRANULOMA VENEREUM (LGV)

DEFINITION
LGV is a sexually transmitted infection (STI) caused by the L1, L2 and L3 serovars of *Chlamydia trachomatis*.

CLINICAL FEATURES
It presents with a transient genital ulcer and inguinal lymphadenitis (bubo) which is usually unilateral and becomes fluctuant. The genito-anorectal syndrome presents with lower abdominal pain and dyspareunia in females and in men who have sex with men (MSM). The most common clinical manifestation of LGV among heterosexuals is tender inguinal and/or femoral lymphadenopathy that is typically unilateral. A self-limited genital ulcer or papule sometimes occurs at the site of inoculation. However, by the time patients seek care, the lesions have often disappeared. Rectal exposure in women or MSM can result in proctocolitis, including mucoid and/or haemorrhagic rectal discharge, anal pain, constipation, fever, and/or tenesmus.

LABORATORY TESTS
- Serological tests (LGV CFT): single titre of 1:64 or more is significant or a rising titre over 2 weeks with the appropriate clinical presentation
- Culture of the chlamydial organism from lymph node aspiration
- NAATs for Chlamydia trachomatis should also be done from the appropriate clinical sites as well as urine.

Screening for HCV & HIV is also encouraged

TREATMENT
Local Treatment
Aspirate the fluctuant buboes. Insert needle through healthy skin to prevent chronic sinus formation.

Systemic Treatment
Recommended Regimen(s)
1. Doxycycline 100mg orally BD x 3 weeks

Alternative Regimen(s)
1. Azithromycin 1g orally weekly x 3 weeks

or

2. Erythromycin 500mg orally QDS x 3 weeks

FOLLOW-UP
Treatment should be continued till clinical signs improve. Test of cure 4 weeks after completion of treatment can be considered.

MANAGEMENT OF SEXUAL CONTACTS
Persons who have had sexual contact with a patient within 30 days before onset of patient's symptoms should be examined and treated when indicated.

CONSIDERATIONS IN PREGNANCY
Pregnant and lactating women should be treated with erythromycin. Azithromycin may prove useful for treatment of LGV in pregnancy. Tetracycline and doxycycline are contraindicated in pregnant women.

CONSIDERATIONS IN HIV INFECTION
Persons with both LGV and HIV infection should receive the same regimens as those who are HIV-negative. Prolonged therapy may be required, and delay in resolution of symptoms may occur.

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. BASHH. (2013). National Guideline for the Management of Lymphogranuloma Venereum.

3. Radcliff, K. (2001). European STD Guidelines. Int J of STD/AIDS, Vol12:3.

MALE GENITAL SYNDROMES

ACUTE EPIDIDYMO-ORCHITIS

DEFINITION

Acute epididymo-orchitis is a clinical syndrome consisting of pain, swelling and inflammation of the epididymis +/- testes. It is usually caused by either sexually transmitted pathogens ascending from the urethra or non-sexually transmitted uropathogens spreading from the urinary tract. Acute epididymitis caused by sexually transmitted enteric organisms (e.g. *Escherichia coli*) also occurs among men who are the insertive partner during anal intercourse.

Historically, sexually transmitted infections have been attributed as the predominant cause for epididymitis in the <35 age group and enteric pathogens in the >35 age group. However, evidence to support this approach is limited; age and sexual history taking are not sufficient for guiding antibiotic therapy alone.

Sexually acquired pathogens

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- *Mycoplasma genitalium*

Non-sexually acquired pathogens

- Gram negative enteric organisms: risk factors include obstructive urinary disease, urinary tract surgery or instrumentation
- Mumps (most common cause of isolated orchitis): ask for history of mumps vaccination (MMR)
- Others including *M. tuberculosis*

Non-infectious causes of testicular pain

- Trauma
- Testicular torsion: sudden onset of severe pain, absence of urethritis or urine abnormalities, younger patients

CLINICAL FEATURES

Symptoms

- Acute onset, usually unilateral scrotal pain +/- swelling
- Urethritis: urethral discharge, dysuria, penile irritation; but patients can be asymptomatic
- Urinary tract infection: dysuria, frequency, urgency

Signs

- Typically features unilateral swelling and tenderness of epididymis +/- testes, usually beginning in the tail of the epididymis and spreading to involve the whole of the epididymis and testes
- Other signs include urethral discharge, hydrocele, erythema +/- oedema of scrotum, pyrexia

DIAGNOSIS

Acute epididymo-orchitis due to sexually acquired pathogens is suspected in the following situations:

- Characteristic unilateral scrotal pain and swelling of relatively acute onset
- Palpable tender swelling of the epididymis starting with the tail at the lower pole of the testis and spreading towards the head at the upper pole of the testis +/- involvement of the testicle
- Sexually active male below 35 years of age
- Recent sexual exposure (within 4 to 6 weeks)
- Multiple sex partners
- Recent treatment for urethritis
- Presence of symptoms or signs or microscopic evidence of urethritis
- No recent history of urinary tract infection, urogenital surgery, catheterisation or instrumentation
- No past history of urogenital abnormalities or pathology
- Torsion of the spermatic cord (testicular torsion) is the most important differential diagnosis

DIFFERENTIAL DIAGNOSES OF TESTICULAR ENLARGEMENT AND SCROTAL SWELLING

- Testicular torsion
  - This is a surgical emergency. It should be considered in all patients and should be excluded first as testicular salvage **IS REQUIRED WITHIN 6 HOURS.** Salvage becomes decreasingly likely with time.
  - The testis may be swollen, tender, high-riding with a horizontal lie. The cremasteric reflex is also absent.
  - Torsion is more likely if:
    - The patient is under 20 years (but can occur at any age)
    - The pain is sudden (within hours)
    - The pain is severe
    - Preliminary tests do not show urethritis or likely urinary tract infection
- Spermatocele
- Hydrocele
- Testicular trauma
- Indirect inguinal hernia
- Testicular cancer

INVESTIGATIONS

- Urethral Gram-stained smear
- First void urine (FVU) or urethral smear for NAAT (*C. trachomatis* and *N. gonorrhoeae*)
- Mid-stream urine (MSU): microscopic examination and culture

All patients with sexually transmitted epididymo-orchitis should be screened for other STIs.

All patients with urinary tract pathogen confirmed epididymo-orchitis should be investigated for structural abnormalities and urinary tract obstruction by a urologist.

TREATMENT

As identification and isolation of causative agents may not be always easy and immediate, all patients with acute epididymo-orchitis suspected to be sexually-acquired should be treated with drugs that are effective against both gonococcal and chlamydial infections, as they may occur concurrently. Empiric therapy is indicated before laboratory test results are available.

Recommended Regimen(s)

Infections due to sexually-transmitted pathogens

First line choice:

1. Ceftriaxone 500mg IM daily x 1-3 days **[III, B]**
   plus
   Doxycycline 100mg orally BD x 10-14 days **[III, B**]

*In patients who also practice insertive anal sex and are at risk for enteric organisms, consider adding on ofloxacin (see below).

Second line choice:

1. Levofloxacin 500mg orally daily x 10 days **[III,B]**

   or

2. Ofloxacin 200mg orally BD x 14 days **[II,B]**

Infections due to non-sexually-transmitted pathogens

1. Ofloxacin 200mg orally BD x 10-14 days **[IIb, B]**

   or

2. Ciprofloxacin 500mg orally BD x 10-14 days **[Ib, A]**
   if enteric organisms are suspected, or if patient is allergic to cephalosporins or tetracyclines

Adjunctive therapy includes bed rest, scrotal elevation and analgesia e.g. NSAIDS. Corticosteroids have not been shown to be useful.

FOLLOW-UP
If there is no improvement in the patient's condition after 3 days, the diagnosis should be reassessed and therapy re-evaluated. Further follow-up is recommended at 2 weeks to assess compliance with treatment, partner notification and improvement of symptoms. Where there is little improvement, further investigations such as an ultrasound scan or surgical assessment should be considered.

MANAGEMENT OF SEXUAL CONTACTS
All sex partners of patients with sexually-transmitted epididymo-orchitis within the preceding 60 days should be referred for examination and treated where indicated.

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. IUSTI 2016 European Guideline on the management of epididymo-orchitis. Retrieved from: https://www.iusti.org/regions/Europe/pdf/2017/EOguideline220117.pdf

NON-GONOCOCCAL URETHRITIS (NGU)

DEFINITION

NGU is diagnosed when examination findings or microscopy indicate inflammation without the presence of Gram-negative intracellular diplococci.

AETIOLOGICAL AGENTS

- *C. trachomatis* accounts for up to 50% of cases
- *M. genitalium* may account for 15-20% of cases
- Other mycoplasmas and ureaplasmas: unclear role
- *T. vaginalis*
- *N. meningitides*
- HSV, EBV, and adenovirus are less common pathogens
- Enteric bacteria have been identified as an uncommon cause of NGU and might be associated with insertive anal intercourse
- Urinary tract infection is implicated in up to 6.4% of cases (only evaluated as a cause in 1 study)
- Studies have shown that no pathogens may be isolated in up to 50% of the cases.

CLINICAL FEATURES

- Symptoms: Urethral discharge, dysuria, penile irritation, or asymptomatic
- Signs: Urethral discharge. This may not have been noticed by the patient or may only be present on urethral massage. Examination may also be normal.
- Complications: Epididymo-orchitis and sexually acquired reactive arthritis / Reiter's syndrome. These are infrequent, occurring in fewer than 1% of cases. Increased genital shedding of HIV may also occur.

DIAGNOSIS

Screening Tests

1. Gram-stain urethral smear
    - Specimen taken 4 hours after last micturition
    - Polymorphonuclear leukocyte count (PMNL) ≥ 5 per high power (x1000) microscopic field (averaged over five fields with greatest concentration of PMNLs)

1. Gram-stain preparation from centrifuged sample of First Pass Urine (FPU) specimen
    - ≥10 PMNL per high-power (x1000) microscopic field (averaged over five fields with greatest concentration of PMNLs)

2. Mid-stream urine
    - Should be taken if a urinary tract infection is suspected from the history
    - If the patient complains of severe dysuria, haematuria (microscopic or macroscopic), nocturia, urinary frequency, urgency, or has not been sexually exposed.

There is little justification in performing urethral microscopy in asymptomatic men

Confirmatory NAAT tests

NAAT can be performed on urine samples to identify *C. trachomatis*, *N. gonorrhoeae* or *M. genitalium*.

TREATMENT

General Measures

The following should be discussed and clear written information provided:

- An explanation of the causes of NGU, including non-infective causes, and possible short term and long-term implications for the health of the patient and his partner
- The side-effects of treatment and the importance of compliance with medication
- The importance of their sex partner(s) being evaluated and treated
- Advice to abstain from sexual intercourse, or if that is not possible, the consistent use of condoms, until he has completed therapy and his partner(s) have been treated
- Advice on safer sex
- The importance of any follow-up arrangements
- It is important to note that the inflammatory exudate may persist for an unknown length of time even when the putative organism has been eliminated

Recommended Regimen(s)

1. Doxycycline 100mg orally BD x 7-14 days

Alternative Regimen(s)

1. Azithromycin 500mg orally STAT & 250mg orally daily x 4 days
    - Increased risk of treatment failure if *M. genitalium* present, also risk of inducing macrolide resistance. Single dose azithromycin is <u>not</u> recommended.

or

2. Erythromycin 500mg orally QDS x 14 days
    - Erythromycin might be less efficacious than either doxycycline or azithromycin, mainly because of the frequent occurrence of gastrointestinal side effects that can lead to non-compliance.

or

3. Ofloxacin 200mg orally BD or 400mg orally daily x 7 days

FOLLOW-UP

- Patients are advised to return in 2 weeks for an evaluation of symptoms and signs, test-of-cure, patient education and partner management & screening of other STIs
- HIV and syphilis serology to be repeated at 3 months

MANAGEMENT OF SEXUAL CONTACTS

- All sexual partners at risk within the last 60 days should be assessed and offered epidemiological treatment whilst maintaining patient confidentiality.
- These partners should also be examined to exclude other STIs.
- At least 30% of partners of men with NGU have chlamydial infections of the cervix and such women are at risk of developing upper genital tract infections, which are often asymptomatic and have the potential sequelae of ectopic pregnancy, infertility and pelvic inflammatory disease.

PERSISTENT AND RECURRENT NGU

This is empirically defined as persistent or recurrent symptomatic urethritis occurring 30-90 days following treatment of acute NGU and may occur in 10-20% of patients.

The aetiology is likely multi-factorial.

- Any treatment of persistent NGU should cover *M. genitalium* and *T. vaginalis*, both of which are not covered by initial recommended regimen for NGU.
- Examine the patient specifically to look for intra-meatal warts.
- If dysuria is marked, look for intra-urethral herpes infection.

Diagnosis of Persistent/Recurrent NGU

The patient should have definite symptoms of urethritis, or physical signs on examination.

There should be objective evidence of urethritis e.g. presence of urethral discharge or pus cells on urethral smear.

- Review medication compliance
- Check for re-infection from previous partner: repeat PCRs if necessary
- Check for infection from a new partner: repeat PCRs if necessary
- Suggest screening for all partners
- Screen for *Mycoplasma genitalium*
- Check for symptoms suggestive of urinary tract infection (severe dysuria, haematuria (microscopic or macroscopic), nocturia, urinary frequency, urgency) and perform a urine dipstick or microscopy. If positive, send for urine culture and treat accordingly.

↓

If Doxycycline was prescribed initially

Azithromycin 1g then 500mg x 2 days
+
Metronidazole 400mg orally BD x 7 days

or

If Azithromycin was prescribed initially

Doxycycline 100mg BD x 7 days
+
Metronidazole 400mg orally BD x 7 days

↓

- If *M. genitalium* PCR positive:
  - Refer to *M. genitalium* chapter: Moxifloxacin 400mg daily for 7 days
- Check for re-infection from previous partner: repeat PCR if necessary
- Check for infection from a new partner: repeat PCR if necessary
- If GC/CT/MG PCR negative, consider longer course Doxycycline 100mg BD x 4-6 weeks

Note: If NAAT repeatedly negative, no further antimicrobial treatment. To observe and reassure. Avoid repeated courses of anti-microbials and over-investigation.

↓

- Consider urological referral if there is clincial suspicion of prostatitis, urethral stricture, UTI

Explain and reassure the patient that:

- The physical sequelae of persistent NGU such as infertility are slight
- The risk of transmission is low because repeated courses of antibiotics would have eliminated infective causes
- Even without treatment, symptoms will usually resolve with time
- Most of the recurrences may arise independent of resumption of sexual activity

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. BASHH UK National Guidelines for the management of non-gonococcal urethritis (updated Dec 2018), retrieved from https://www.bashhguidelines.org/guidelines

3. IUSTI 2016 European Guideline on the management of non-gonococcal urethritis. Retrieved from https://www.iusti.org/regions/europe/pdf/2016/2016EuropeanNGUGuideline.pdf

PROSTATITIS

1. ACUTE PROSTATITIS

Acute prostatitis is caused by urinary tract pathogens. These include gram-negative organisms: most commonly *Escherichia coli*, *Proteus* spp, *Klebsiella* spp and *Pseudomonas* spp; Enterococci; *Staphylococcus aureus*; rarely anaerobes such as *Bacteroides* spp. Acute prostatitis is an uncommon complication of urinary tract infections. Consider co-management with a urologist.

CLINICAL FEATURES

Acute prostatitis is an acute severe systemic illness.

Symptoms

- UTI: dysuria, frequency and urgency
- Prostatitis: low back pain, perineal, penile and sometimes rectal pain
- Bacteraemia: fever and rigors; arthralgia and myalgia may occur

Signs

- Localised to the prostate: an extremely tender, swollen and tense, smooth textured prostate gland which is warm to the touch
- Bacteraemia: pyrexia and tachycardia

Complications

- Acute retention of urine (ARU) secondary to prostatic oedema
- Prostatic abscess, bacteraemia, epididymitis and pyelonephritis.

DIAGNOSIS

- Mid-stream urine sample for dipstick testing, culture for bacteria and antibiotic sensitivity
- Blood cultures for bacteria and antibiotic sensitivity
- Prostatic massage should not be performed. It is extremely painful and may possibly precipitate bacterial dissemination and is of little benefit as pathogens are almost always isolated from urine

TREATMENT

General Measures

Adequate hydration should be maintained, rest encouraged and analgesia prescribed such as NSAIDs, after ruling out acute kidney injury.

- Empirical therapy should start immediately, and adjusted according to sensitivity results
- Parenteral or oral treatment should be selected according to the clinical condition of the patient. If there is deterioration or failure to respond to oral therapy, urgent admission and parenteral therapy should be arranged.
- If ARU occurs, suprapubic catheterisation should be performed to avoid damage to the prostate.

Recommended Regimen(s)

For patients requiring parenteral therapy, antibiotics covering the likely organisms should be used:

- Ciprofloxacin or levofloxacin (quinolones)
- Cefuroxime or ceftriaxone (second or third generation cephalosporins)
- Piperacillin with tazobactam (a broad-spectrum penicillin)
- Gentamicin or amikacin (aminoglycosides)

Oral therapy

1. Ciprofloxacin 500mg orally BD x 14-28 days **[IV, C]**

   or

2. Ofloxacin 200mg orally BD x 14-28 days **[IV, C]**

   or

3. Co-trimoxazole (trimethoprim/sulfamethoxazole) 160/800mg (2 tabs) orally BD x 14-28 days for patients intolerant of or allergic to quinolones.

MANAGEMENT OF SEXUAL CONTACTS
Treatment of sexual partners is not required as it is caused by uropathogens.

FOLLOW-UP
If there is no response after 48 hours of taking an antibiotic, the patient should be referred to hospital because of concerns around complications, such as such as acute urinary retention or prostatic abscess, and treatment failure because of resistant bacteria.

A minimum of a 14-day course of all the recommended antibiotics was required for acute prostatitis. At 14 days, treatment should be reviewed, and either stopped or continued for a further 14 days as needed.

2. CHRONIC PROSTATITIS

Chronic prostatitis can be differentiated into the following:

- Chronic bacterial prostatitis (CBP)
- Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)
    - Inflammatory
    - Non-inflammatory

These are symptomatic, chronic forms of prostatitis and co-management with urology is suggested.

The diagnosis of CBP requires the presence of (typically recurrent) UTI and isolation of an aetiologically recognised organism from prostatic fluid or urine. The usual causative bacteria are those causing urinary tract infection, most commonly *Escherichia coli*. Some Gram positive organisms such as *Staphylococcus aureus* and *Enterococcus faecalis* may cause CBP.

In contrast, there is no 'gold standard' for a definitive diagnosis of CP/CPPS, which is typically based on patient history, symptoms and exclusion of other causes.

Patients can be considered to be in the:

1. Early stages of the disease if they have experienced persistent, recurrent symptoms for <u>≤6 months</u> and are antibiotic-naïve

2. Later stages of the disease if they have experienced persistent, recurrent symptoms for <u>>6 months</u> and are refractory to initial lines of pharmacotherapy

CLINICAL FEATURES
<u>Symptoms</u>
There are 4 main groups of symptoms:

1. Pain or discomfort in one or multiple urogenital regions
    - Perineum (63%), suprapubic region, testicles/penis (especially penile tip pain), lower back, abdomen, inguinal region, rectum
    - Pain on urination, or that increases on urination
    - Pain during or after ejaculation
    - Neuropathic pain

2. Urinary symptoms
    - Voiding LUTS (Lower Urinary Tract Symptoms)
    - Storage LUTS (urgency +/- urge incontinence, increased urinary frequency, nocturia, dysuria)
    - Urethral burning during and independent of urination
    - Hematospermia
    - Recurrent UTI (more applicable to CBP)

3. Sexual Dysfunction symptoms
    - Decreased libido and erectile dysfunction

4. Psychosocial dysfunction
    - Anxiety/stress/depression

Signs

1. Digital Rectal Examination
    - Including assessment of external genitalia and pelvic floor muscle dysfunction
    - Prostate may be enlarged, tender or normal

2. Abdominal Examination
    - The bladder may be palpable due to urinary retention
    - Exclude other causes of abdominal pain

INVESTIGATIONS

- Urine dipstick test or microscopy (for evidence of urinary tract infection or haematuria).
- MSU: urine cultures may be sterile unless an acute urinary tract infection is present
- 2 or 4 glass test: expressed prostatic secretions and urine obtained after prostatic massage show bacterial colony counts that are at least 10-folds higher than bladder urine samples
- PSA testing: to exclude prostate cancer
- STI screen

Optional Investigations

1. Uroflometry, retrograde urethrography or cystoscopy
    - to exclude bladder outlet obstruction bladder neck stenosis or urethral stricture)
2. MRI or prostate biopsy or Transrectal ultrasound of the prostate (TRUS) biopsy
    - If prostate cancer/abscess suspected

MANAGEMENT

General Measures

Patients should be advised on the underlying causes of CBP and CP/CPPS to help improve their understanding. This may include basic pelvic anatomy and the chronic pain cycle.

Treatment Strategies

1. Alpha adrenergic agonists

- Should be considered in patients who present with significant voiding LUTS (slow urinary flow, hesitancy)
- If no relief from voiding symptoms or other symptoms of CBP or CP/CPPS is achieved within 4-6 weeks, treatment should be stopped and a different pharmacotherapy considered.
- Due to the adverse side-effect profiles of this class of drugs, consider offering uroselective α-adrenergic antagonists (e.g. tamsulosin, alfuzosin and silodosin) as first-line treatment in patients with CBP and CP/CPPS who present with voiding LUTS **[V]**

2. Antibiotics

- Antibiotic treatment should be chosen according to bacterial cultures and sensitivities.
- For patients with early-stage CBP and CP/CPPS, offer a quinolone (e.g. ciprofloxacin or ofloxacin) for 4-6 weeks as first-line therapy
- A repeated course of antibiotic therapy (4-6 weeks) should be offered only if a bacterial cause is confirmed or if there is a partial response to the first course
- If a bacterial cause is excluded (e.g. via urine dipstick or culture) and symptoms do not improve after antibiotic therapy, a different treatment method or referral to specialist care should be considered
- For those allergic to quinolones or in patients recommended to avoid quinolones (epilepsy or prone to seizures) treatment should be selected according to antibiotic sensitivities of the bacterial isolate, and an antibiotic with good penetration into the prostate should be chosen.
- Options include:
    1. Minocycline 100mg orally BD x 28 days **[III, B]**
       **In practice most experts would use doxycycline 100mg orally BD for 28 days because of more toxicity with minocycline.*

       or

2. Trimethoprim 200mg orally BD x 28 days **[IV,B]**

3. Pain management

- In patients with early-stage disease who present with pain symptoms, regular paracetamol may be offered
- NSAIDs should be offered only for short-term treatment of pain, to patients with early-stage CBP or CP/CPPS whose symptoms are suspected to be due to an inflammatory process, or those judged to be experiencing an inflammatory flare. These patients should be under regular review by a GP.
- To prevent unwanted adverse effects, NSAIDs should be stopped within 4-6 weeks of treatment initiation if they do not reduce symptoms.
- In patients with early-stage CBP or CP/CPPS, use of opioids for pain management should be avoided, due to the risk of dependency.
- If pain is considered to be neuropathic in origin, treatment with a gabapentinoid (e.g. pregabalin or gabapentin), a tricyclic antidepressant (e.g. amitriptyline, nortriptyline or trimipramine)

There is insufficient evidence to warrant recommending surgical techniques, including radical prostatectomy, TURP, HIFU or prostatic massage for the treatment of CBP or CP/CPPS, except in the context of a clinical trial setting.

References:

1. Consensus Guideline for Chronic Prostatitis and Chronic Pelvic Pain Syndrome from Prostate Cancer UK [2015] Retrieved from: https://www.bashhguidelines.org/media/1065/bju-prostatitis-2015.pdf

2. Acute prostatitis: antimicrobial prescribing NICE guideline [2018]. Retrieved from https://www.nice.org.uk/guidance/gid-apg10007/documents/draft-guideline-2

MOLLUSCUM CONTAGIOSUM

DEFINITION
Molluscum contagiosum is a viral infection caused by a pox virus. Genital molluscum infections in adults are usually sexually transmitted.

CLINICAL FEATURES
Individual lesions of molluscum contagiosum are discrete, smooth, pearly or flesh-coloured, dome-shaped papules and are often confined to the genital area. Each papule may have a mildly erythematous base and a central punctum beneath which lies a white curd-like core.

In patients with extensive facial lesions, HIV screening should be considered. In immunocompromised patients, lesions may become large, exuberant, and unsightly and secondary infection may be a problem. In immunocompromised patients, cutaneous lesions of infections such as histoplasmosis, penicilliosis or cryptococcosis can also resemble molluscum

LABORATORY TESTS
Diagnosis is mainly clinical. However, Giemsa-stained smears of the expressed core from the punctum will reveal molluscum bodies. In ambiguous cases, a skin biopsy will also demonstrate molluscum bodies.

TREATMENT
Recommended Therapy
- Deroof the lesion with a sharp curette, a comedone extractor or a needle
- Destroy the remaining lesion with liquid nitrogen, trichloroacetic acid application or electrocautery **[IV, C]**
- More than one treatment session may be required

Alternative Therapy
- Topical retinoid such as topical tretinoin 0.05% cream BD
- Topical salicylic acid once a night
- Topical imiquimod 5% cream three times a week has been tried as off-label use for genital and non-genital molluscum

MANAGEMENT OF SEXUAL CONTACTS
Regular sex partners should be encouraged to come for examination and treatment, where indicated.

References:
1. Hengge, U.R., & Cusini, M. (2003). Topical |mmunomodulators for the Treatment of External Genital Warts, Cutaneous Warts and Molluscum Contagiosum. Br J Dermatol, 149 Suppl 66:15-9.

2. Tan, H.H., Goh, C.L. (2006). Viral Infections Affecting the Skin in Organ Transplant Recipients: Epidemiology and Current Management Strategies. Am J Clin Dermatol, 7: 13-29.

3. Van der Woudon JC, Van der Sande R, Van Suiklekom-Smit LWA, et al. Interventions for cutaneous molluscum contagiosum. The Cochrane Colloboration 2009. Wiley

MYCOPLASMA GENITALIUM

INTRODUCTION

Mycoplasma genitalium, the smallest known self-replicating bacterium currently, is increasingly the cause of non-gonococcal urethritis (NGU) in men and an increasingly recognised cause of cervicitis and pelvic inflammatory disease (PID) in women.

It is a member of the *Mycoplasmataceae* family and *Mollicutes* class of bacteria. It is not visible on Gram-stain as it lacks a cell wall. Isolating *M. genitalium* is extremely challenging as it is a fastidious organism and may require more than one month to grow.

M. genitalium has been isolated from multiple tissue sites but its association with clinical disease appears to be limited to the urogenital tract. Studies in both male and female non-human primates, in which genital infection developed following urogenital inoculation of *M. genitalium*, demonstrate its pathogenicity. *M. genitalium* can persist for months or years in infected individuals.

DIAGNOSIS

In the clinical setting, the microbiological diagnosis of *M. genitalium* is infrequently made because of the absence of commercially-available, FDA-cleared diagnostic tests. However, if available, the diagnosis of *M. genitalium* infection may be made through detection of the organism using nucleic acid amplification tests (NAAT). The preferred specimens are a first-void urine sample in men/women and a cervical swab in women.

DIAGNOSTIC TESTS

NAATs are the only clinically useful method of detecting *M. genitalium* but are not widely available locally; the DSC clinic provides a PCR test with a turn-around-time of 7 working days. There are no standardised serological tests for *M. genitalium*.

ANTI-MICROBIAL SUSCEPTIBILITY

The lack of a cell wall renders *M. genitalium* resistant to antibiotics which target cell wall synthesis, such as penicillins and other beta-lactams. *M. genitalium* is generally susceptible in vitro to the macrolides (azithromycin > erythromycin and clarithromycin), fluoroquinolones, tetracyclines, and clindamycin, although resistance is a growing issue.

Azithromycin has at least 100-fold more activity against this organism than the tetracyclines or most fluoroquinolones. However, strains of *M. genitalium* with resistance to azithromycin are increasingly reported following the use of single dose azithromycin in patients with non-gonococcal urethritis (NGU). In addition, reports of mutations in *M. genitalium* genes parC and gyrA, which are associated with fluoroquinolone resistance, have also surfaced.

There are no commercially available resistance tests in Singapore for *M. genitalium* at the moment.

CLINICAL APPROACH

Clinical suspicion of infection by *M. genitalium* should be high, and treatment can be given empirically even before laboratory confirmation. Our approach to therapy of *M. genitalium* depends on the timing of presentation, the availability of *M. genitalium* PCR testing, and the treatment history. Treatment for *M. genitalium* can be considered in patients with NGU or MPC with a negative chlamydial PCR who continue to have symptoms & signs.

TREATMENT

Empiric treatment for urethritis, cervicitis, and pelvic inflammatory disease (PID) includes therapy for *C. trachomatis* with doxycycline or azithromycin. Both agents have activity against *M. genitalium*, although clinical evidence suggests that azithromycin is superior to doxycycline. However high rates (50%) of macrolide resistance and fluoroquinolone mutations (20%) in *M. genitalium* have been reported.

Recommended Regimen(s)
Dependent on previous treatment & resistance testing.

Macrolide resistant OR resistance testing not available OR failed macrolide treatment

1. Doxycycline 100mg orally BD x 7 days followed by moxifloxacin 400mg orally daily x 7 days

Macrolide sensitive

1. Doxycycline 100mg orally BD x 7 days

   followed by
   Azithromycin 1g orally STAT then 500mg orally daily x 3 days

Failed macrolide and fluoroquinolone treatment

1. Minocycline 100mg orally BD x 14 days

or

2. Doxycycline 100mg orally BD x 10 days *plus* pristinamycin 1g TDS x 10 days

or

3. Pristinamycin 1g orally QDS x 10 days

Complicated infection (PID/epididymo-orchitis)

3. Moxifloxacin 400mg orally daily x 14 days

MANAGEMENT OF SEXUAL CONTACTS
Although there are no guidelines for partner referral and treatment, it is reasonable to screen all sexual partners of laboratory-confirmed cases of *M. genitalium* and treat if positive. If screening of sexual partners of index patients with confirmed *M. genitalium* is not possible, empirically treating for *M. genitalium* given the evidence of sexual transmission of this organism. Although the incubation period of this pathogen remains undefined, screening should target sexual partners in the past 60 days.

CONSIDERATIONS IN PREGNANCY
Data on *M. genitalium* and its association with adverse pregnancy outcomes are limited, however it has been associated with a small increased risk of preterm delivery and spontaneous abortion. Azithromycin use during pregnancy is unlikely to increase the risk of birth defects or adverse pregnancy outcomes. A 3-day course of azithromycin can be used for uncomplicated *M. genitalium* infection detected in pregnancy. The use of moxifloxacin in pregnancy is contra-indicated. In women with likely macrolide resistance, or with upper genital tract infection in pregnancy, options are limited. There are no data regarding the use of pristinamycin in pregnancy. An informed discussion should be had with the pregnant woman around the risks associated with the use of these drugs in pregnancy and the risks of adverse outcomes associated with *M. genitalium* infection, and where possible treatment should be delayed until after pregnancy.

TEST OF CURE AND FOLLOW-UP
Early testing after treatment when DNA load is low can give false negative results. We recommend all patients should attend for a TOC five weeks (and no sooner than three weeks) after the start of treatment to ensure microbiological cure and to help identify emerging resistance. Clinical cure (i.e. resolution of symptoms) should be established at the TOC visit. The risk of re-infection should be excluded and compliance with medication should be verified.

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. BASHH (2018) National Guideline for the management of infection with Mycoplasma genitalium.

3. Doyle M et al Non-quinolone Options for the Treatment of Mycoplasma genitalium in the Era of Increased Resistance from Open Forum Infectious Diseases 2020

4. Read TRH Use of Pristinamycin for Macrolide-resistant Mycoplasma genitalium infection Emerging Infectious Diseases Vol 24 No 2, Feb 2018 328-35

PEDICULOSIS PUBIS

DEFINITION
Pediculosis pubis is an infestation of the anogenital region by the crab louse, *Pthirus pubis*. In adults, it is often sexually transmitted.

CLINICAL FEATURES
The infestation is clinically diagnosed by the presence of brown adult lice on the pubic hair, body hair and rarely, eyebrows and eyelashes. There may also be the presence of eggs (nits) which adhere to the hairs. Small haemorrhagic spots may also be seen on the pubic/genital skin and underclothing. Blue macules (maculae caeruleae) may be visible at feeding sites. There may be no symptoms or there may be itch due to sensitivity to the feeding lice.

LABORATORY TESTS
The presence of lice or nits recovered from pubic hair (by microscopy) confirms the diagnosis.

TREATMENT
Recommended Regimen(s)

1. Malathion 0.5% lotion application. Wash off after 12 hours. **[IV, C]**

   or

2. Permethrin (1%) cream rinse, washed off after 10 minutes, can also be used, but is currently unavailable in Singapore. **[IV, C]**

Alternative Regimen(s)

1. Ivermectin 250 mcg/kg orally once, repeat in 2 weeks

Special Considerations
If the eyelashes are affected, apply an occlusive ophthalmic ointment or Vaseline to the eyelid margin twice daily for 10 days and/or remove lice with tweezers or forceps **[IV, C]**

Pregnant or lactating women should be treated with permethrin and NOT malathion.

FOLLOW-UP
Patients should be re-evaluated after 7 days (the time taken for any nits to hatch into lice). Re-treat only if the lice are found or eggs are observed. Clothing and bed sheets that have been contaminated should be washed in hot water.

MANAGEMENT OF SEXUAL CONTACTS
Regular sex partners within the last month should be encouraged to attend for examination and treatment.

References:

1. Chosidow, O. (2000). Scabies and Pediculosis. Lancet, 355(9206):819-26. Retrieved from, PubMed.

2. Meinking, T.L., Serrano, L., Hard, B., Entzel, P., Lernard, G., Rivera, E., et al. Comparative in Vitro Pediculicidal Efficacy of Treatments in a Resistant Head Lice Population in the United States. (2002). Arch Dermatol, 138:220-4. Retrieved from, PubMed.

3. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

SCABIES

DEFINITION
Scabies is an infestation by the mite, *Sarcoptes scabiei* var. *hominis*.

CLINICAL FEATURES
The clinical features of scabies are pruritic papules on the genitals, finger webs, wrists, axillae and buttocks. There is nocturnal exacerbation of the itch. Family members and sexual partners may have similar symptoms. The presence of typical symptoms and signs is sufficient to make the diagnosis, even if skin scrapings are negative.

LABORATORY TESTS
The mite can be demonstrated by microscopic examination of scrapings from burrows on the skin.

TREATMENT
Recommended Regimen(s)

1. Malathion 0.5% lotion applied thinly to all areas of the body from the neck down and washed off after 24 hours. Apply nightly x 2 nights. **[IV, C]**

or

2. Permethrin lotion (only available at NSC pharmacy) overnight application. Suitable for pregnant women and children less than 1-year-old

Alternative Regimen(s)

Topical

1. Emulsion benzyl benzoate (EBB) 25% application for adults and 10% for children under 10 years old (but older than 2-year-old). Apply nightly from neck down on all areas of body for 3 nights **[IV, C]**

or

2. Sulphur compounds, 6% in aqueous cream. Apply before bed time and wash off the following morning. Repeat x 5 days.

Oral/Systemic

1. Ivermectin **[Ib, A]**
   Several controlled trials have assessed the efficacy of a single dose of ivermectin 200 mg/kg or 0.2mg/kg for the treatment of scabies. A second dose may be given 1-2 weeks later.

   This should not be routinely used as first-line therapy. Oral ivermectin should be considered for patients who failed treatment and also in patients with crusted scabies. There was a previous controversial report of excess risk of death for elderly patients, which has not been confirmed. Several other studies of ivermectin have shown that it is safe in children as well as older patients. Consulting an expert before use is recommended. Ivermectin is not for use in pregnancy.

Pregnant Patients

1. Permethrin lotion (only available at NSC pharmacy) overnight application

or

2. Sulphur compounds, 6% in aqueous cream. Apply before bed time and wash off the following morning. Repeat x 5 days.

CRUSTED (NORWEGIAN) SCABIES

- Usually in the malnourished, immunocompromised and patients with neurological disturbance.
- Intensive topical treatment is required.
- Combined topical and oral treatment with ivermectin (0.2 mg/kg) may also be considered.
- Occasionally, in-patient treatment may be beneficial.

FOLLOW-UP

Clothing and bed sheets should be washed with hot water or dry cleaned. Patients must be warned that there might be an initial exacerbation of the pruritus. Antihistamines are required to relieve the itch.

Repeat treatment with a different agent is often necessary; treatment failure may be due to resistance to medication, faulty application techniques, poor penetration through thick scales, mites in difficult to reach areas, and reinfection.

Post-scabietic itch may last for several weeks and is treated with topical corticosteroids and antihistamines.

MANAGEMENT OF SEXUAL CONTACTS

Sex partners and close family contacts and all members of the household should be treated even if asymptomatic.

References:

1. Chosidow, O (2006). Scabies. N Engl J Med, 354: 1718-27. Retrieved from, NEJM.

2. CDC (Centers for Disease Control and Prevention) guidelines - Scabies - Resources for Health professionals - Medications (2017, august 9). Retrieved from https://www.cdc.gov/parasites/scabies/health_professionals/meds.html

3. Strong, M., and P. Johnstone. “Interventions for Treating Scabies.” Cochrane Database of Systematic Reviews , no. 3 (July 18, 2007): CD000320.

SEXUAL ASSAULT AND STI EVALUATION

INTRODUCTION

These guidelines are predominantly limited to the identification, prophylaxis, and treatment of sexually transmitted infections (STIs) and conditions among adolescent and adult female sexual assault survivors. Some of the guidelines apply to male sexual assault victims. The detailed & specific documentation of physical findings, specimen collection for forensic and legal purposes is beyond the scope of these guidelines. Patients who request forensic examination should be referred to a dedicated sexual assault service (e.g. One-Stop Abuse Forensic Examination (OneSafe) Centre, Cantonment Complex) or the police.

Management will vary depending on when the assault occurred and includes:

- Allowing the patient to accept or decline medical management/treatment, or referral to sexual assault service/police for forensic examination.
- Forensic examination, if a recent assault, needs to be performed by an appropriately trained clinician as soon as possible after the assault, preferably within 72 hours.
- Discussion and provision of medical treatment options: emergency contraception, post-exposure prophylaxis, STIs/HIV screening and treatment.
- Referral for individual and/or support to sexual assault counsellors.
- Follow-up: patients may need to return for management and follow-up at 2, 4 and 12 weeks depending on when the assault occurred.

Notes

1. Some STIs e.g. gonorrhoea, chlamydia and syphilis are almost exclusively transmitted sexually; others e.g. bacterial vaginosis and candidiasis may be transmitted non-sexually.
2. The presence of STIs after the assault may represent pre-existing infection and may not be the result of the assault.
3. The decision to obtain genital or other specimens for STI diagnosis should be made on an individual basis.

INITIAL EXAMINATION

- Assess injury healing, if relevant.
- NAATs for *C. trachomatis* and *N. gonorrhoeae* at the sites of penetration or attempted penetration. These should be repeated if initial baseline tests are negative or performed <2 weeks after exposure.
- NAATs from a urine or vaginal specimen from a vaginal specimen for *T. vaginalis*. Point-of-care testing and/or wet mount with measurement of vaginal pH and KOH application for the whiff test from vaginal secretions should be done for evidence of BV and candidiasis, especially if vaginal discharge, malodour, or itching is present.
- A serum sample for evaluation of HIV, hepatitis B, and syphilis infections. Consider hepatitis C testing.
- Pregnancy test if sexual assault >2 weeks prior to presentation.

FOLLOW-UP AT 2 WEEKS

- Test results, treatment based on laboratory findings, pregnancy test, assess healing, coping
- Follow-up testing for chlamydia, gonorrhoeae, trichomonas

FUTURE FOLLOW-UP

- 3 months: Blood tests for HIV and syphilis
- 6 months: Consider hepatitis C testing

TREATMENT

Epidemiological Treatment

If follow-up cannot be assured, the following regimen of epidemiological treatment for can be used:

1. Ceftriaxone 500mg IM once
   plus
   Doxycycline 100mg orally BD x 7 days
   plus
   Metronidazole 2g orally once

Other Considerations

Emergency contraception

For rape occurred within 72 hours (up to 5 days)

- Levonorgestrel 1.5mg STAT or Ulipristal 30mg STAT, or
- IUCD insertion

Hepatitis B vaccination

Consider post-exposure hepatitis B vaccination (without HBIG) if the hepatitis status of the assailant is unknown and the patient not previously vaccinated. This should be administered at the initial examination, and follow-up doses at 1-2 and 4-6 months after the first dose. Patients previously vaccinated but not tested for immunity may be given a vaccine booster dose. (Refer to Chapter on Viral Hepatitis)

HIV Post-Exposure Prophylaxis (PEP)

HIV PEP should be discussed, documented and offered depending on the risk assessment as soon as possible after unprotected exposure but no later than 72 hours after sexual assault. (Refer to chapter on HIV Post-Exposure Prophylaxis)

References:

1. BASHH. (2012). United Kingdom National Guidelines on the Management of Adult and Adolescent Complainants of Sexual Assault.

2. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

STI SCREENING FOR SPECIAL POPULATIONS

STI SCREENING OF MEN WHO HAVE SEX WITH MEN (MSM)

INTRODUCTION

MSM are at high-risk for HIV infection and other viral and bacterial STIs. The frequency of unsafe sexual practices, the rates of bacterial STIs and incidence of HIV infection have been increasing in MSM. More common STIs include syphilis, gonorrhoea and chlamydia. The underlying behavioural changes may be related to effects of improved HIV/AIDS therapy on quality of life and survival ("safer sex burnout") trends in recreational substance abuse. In addition to that are changes in sex partner networks resulting from new venues for partner acquisition.

Assessment includes routinely enquiring about the sex of patients' sex partners. MSM, including those with HIV, should routinely undergo straightforward, non-judgmental STI/HIV risk assessment and client-centred prevention counselling to reduce the likelihood of acquisition or transmission of HIV and other STIs. Clinicians should be familiar with local community resources available to assist MSM at high risk in facilitating behavioural change and contact tracing. In addition, screening for STIs should be performed. The following screening recommendations should be performed at least annually for sexually active MSM.

SCREENING RECOMMENDATIONS FOR SEXUALLY ACTIVE MSM

Frequency of Screening

- Annually (minimum)
- 3 monthly in high-risk MSM, where high-risk is defined by:
    - any unprotected anal sex
    - >10 partners in 6 months or group sex
    - use of recreational drugs during sex

Serology

- HIV serology, if HIV-negative or not previously/recently (3-6 months) tested
- Syphilis serology (should be part of routine HIV monitoring in HIV positive MSM)
- Hepatitis A, if not previously immunised or tested immune*
- Hepatitis B, if not previously immunised or tested immune/infected*
- Hepatitis C, if any history of injection drug use or if HIV positive
- Type-specific serologic test for HSV-2 may be considered but HSV-2 treatment has not been shown to reduce HIV acquisition

***Note**: If not immune, MSM should be vaccinated for hepatitis A and B. Once the primary vaccination schedule has been completed in immunocompetent MSM, further serology and booster doses are not necessary. In HIV positive MSM, hepatitis B surface antibody levels (Anti-HBs Ab) should be performed annually and a booster dose given if required.

Urine Tests and Swabs

Chlamydia and gonorrhoea PCRs from the

- throat/pharynx
- urethra or first-pass urine is a suitable alternative
- rectum for men who have had receptive anal intercourse, oral-anal sex, receptive fingering or toy insertion

Stool Tests

For MSM patients with diarrhoea, clinicians should consider the risk of enteric pathogens & investigate accordingly with stool cultures.

VACCINATIONS

Vaccination is the most effective means of preventing sexual transmission of hepatitis A and B. Pre-vaccination serologic testing may be cost-effective in some MSM, among whom the prevalence of hepatitis A and B infection may be high, but it should not delay vaccination.

MSM, and especially those who are infected with HIV, are at an increased risk for HPV infection and anal cancer associated with high-risk HPV types. Quadrivalent and 9-valent HPV vaccination may be offered to MSM. Both of these vaccines may also be offered off-label (i.e. aged >26) as they may aid in reducing oral/pharyngeal and anal cancer risk after discussing the risk/benefits with the patient.

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. ASHM STI Management Guidelines on MSM testing advice. Retrieved from http://www.sti.guidelines.org.au/populations-and-situations/msm#testing-advice

3. Clutterbuck D et al 2016 United Kingdom National Guideline on sexual health care of men who have sex with men International Journal of STI & AIDS 0(0) 1-46

STI SCREENING OF TRANSGENDER PATIENTS

INTRODUCTION

Persons who are transgender identify themselves as a gender that is not congruent with the sex they were assigned at birth.

Transgender women ("trans-women" or "transgender male to female") identify as women but were born with male anatomy; similarly, transgender men (also referred to as "trans-men" or "transgender female to male") identify as men but were born with female anatomy. However, transgender persons might use different and often fluid terminology to refer to themselves through their life course.

It is also important to remember that gender identity is independent from sexual orientation. Persons who are transgender might have sex with men, women, or both and consider themselves to be heterosexual, gay, lesbian, or bisexual.

Medical practitioners must be aware of certain sensitivities when addressing transgender patients, including:

1. Create welcoming environments that facilitate disclosure of gender identity & sexual orientation. Be aware that choice of words may be a factor in stigma & discrimination

2. Gender pronouns and sexual identity: ask the patient how they identify and what name and pronouns (he, she, they etc) they wish to use; mirror and echo the terms used by the patient.

3. Discomfort about nomenclature of the genital anatomy: When taking sexual history, using general language can help to increase comfort. For example, say "genitals" rather than naming body parts, as this may trigger dysphoria as many are still uncomfortable with their original biological anatomy. Let your patients know that you are open to using language they feel comfortable with. For example, "frontal hole" is a term sometimes used among trans-men to refer to the vagina.

STI SCREENING

Serologic screening recommendations for transgender people (HIV, Hepatitis B and C, Syphilis) do not differ in recommendations or technique from those for non-transgender people.

The choice of investigations is to be guided by the patient's current anatomy and sexual exposure. Because of the diversity of transgender persons regarding surgical affirming procedures, hormone use, and their patterns of sexual behaviour, clinicians must remain aware of symptoms consistent with common STIs and screen for asymptomatic STIs on the basis of behavioural history and sexual practices.

TRANSGENDER WOMEN

Transgender women may have undergone vaginoplasty (either penile inversion or colo-vaginoplasty). The anatomy of a neovagina created in a transgender woman differs from a natal vagina in that it is a blind cuff, lacks a cervix or surrounding fornices, and may have a more posterior orientation.

Examination may be done with an anoscope instead of a vaginal speculum as it is more anatomically appropriate and comfortable for the patient. The anoscope can be inserted, the trocar removed, and the vaginal walls visualized collapsing around the end of the anoscope as it is withdrawn.

Some surgical approaches include the use of urethral tissue, which could result in mucosal infectious such as chlamydia or gonorrhoea. The risk of infection of intact, inverted penile skin with these organisms is unknown, though lesions such as a syphilitic chancre, herpes or chancroid are possible. When clinically indicated due to symptoms, a physical examination and appropriate testing should be performed.

Screening for cervical HPV is not necessary in these patients without a cervix.

Transgender women who have undergone vaginoplasty retain prostate tissue, therefore infectious prostatitis should be included in the differential diagnoses for sexually active trans women with suggestive symptoms

Most transgender women however, have not undergone genital affirmation surgery and may retain a functional penis; in this instance, they might engage in insertive oral, vaginal, or anal sex with men and women.

TRANSGENDER MEN

Some transgender men retain patent vaginas after metoidioplasty and may require vaginal screening based on sexual history. They may also require screening for cervical cancer and benefit from appropriate vaccination.

Pelvic inflammatory disease (PID) should be in the differential for transgender men with a uterus and fallopian tubes who have vaginal intercourse. Testosterone use is associated with vaginal atrophy; therefore, use of lubricant and a small speculum may be appropriate for pelvic and speculum exams among transgender men with vaginas.

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. Transgender People and STIs - Center of Excellence for transgender Case, UCSF. Retrieved from: http://transhealth.ucsf.edu/trans?page=guidelines-stis

3. Providing appropriate STI care for transgender and gender diverse clients, British Columbia Center for Disease Control. Retrieved from: https://smartsexresource.com/health-providers/blog/201408/providing-appropriate-sti-care-transgender-and-gender-diverse-clients

STI SCREENING OF WOMEN WHO HAVE SEX WITH WOMEN (WSW)

TERMINOLOGY

- WSW: women who have sex with women (description of sexual behaviour/practice).
- Lesbian or bisexual: a woman whose primary sexual and emotional partnerships are with women, or both, respectively (sexual identity as self-identified by the woman).

INTRODUCTION

Women who have sex with women (WSW) are a diverse group with variations in sexual behaviour, identity and risk behaviours. Most WSW report a previous history of sex with men and may continue this practice in the future. Use of barrier protection with female partners (gloves during digital-genital sex, condoms with sex toys, and latex or plastic barriers) is infrequent. Some also report at-risk behaviour such as injecting drug use, history of commercial sex work, and higher risk sexual partners. Clinicians should be aware that sexual orientation is not synonymous with sexual practice, and WSW should not be presumed to be at low or no-risk of STIs and HIV based on sexual orientation alone.

STIs, including HIV, may be transmitted between WSW through the transfer of cervicovaginal fluids during activities involving digital-vaginal or digital-anal contact, and shared penetrative sex toys, and via other sexual practices (e.g., oral-genital/oral-anal sex, direct genital-genital contact).

Clinicians should engage in comprehensive and open discussion about patients' sexual and behavioural risks, and not only about their sexual identity, to accurately assess STI and HIV risk.

All STIs have been reported in varying prevalence in WSW:

- *Trichomonas vaginalis*
- Genital herpes
- Genital warts and cervical HPV infection*
- HIV
- Syphilis
- Gonorrhoea and chlamydia
- Hepatitis B (hepatitis C if a history of injecting drug use)

WSW, therefore, should be screened for STIs and HIV regardless of their sexual practices.

Bacterial vaginosis (BV) is found in high prevalence in WSW, including those in monogamous relationships. However, it is not considered an STI and data are insufficient to support routine screening of BV.

ROUTINE SCREENING TESTS

- Cervical, vaginal or urine NAATs for gonorrhoea and chlamydia
- Genital swabs for bacterial vaginosis, trichomonas and candida in symptomatic WSW
- Serology for HIV and syphilis
- Serology for hepatitis B and offer vaccination if not immune
- Cervical cancer screening tests (cervical cytology*, HPV testing) and offer HPV vaccination, both in accordance with current guidelines.

***Note**: Low and high-grade cervical smear abnormalities have been detected in WSW who reported no previous sex with men. WSW are at risk for acquiring HPV from both their female partners and from current or prior male partners, and thus are at risk for cervical cancer. Therefore, routine cervical cancer screening should be offered to all women, regardless of sexual orientation or sexual practices, and women should be offered HPV vaccine as per current guidelines.

ADVICE ON SAFER SEX PRACTICES

- Condom use with male sex partners (if any)
- Use of dental dams (latex barrier) for oral-genital sex
- Avoid contact with partner's menstrual blood and any visible genital lesions
- Use condoms over penetrating sex toys and a new condom with each new/different partner
- Consider using latex gloves and lubricant for any mutual masturbation that might cause bleeding
- STI and HIV screening, vaccination and contact tracing of partners if diagnosed with an STI

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. Chan SK, Thornton LR, Chronister KJ, et al. Likely female-to-female sexual transmission of HIV - Texas, 2012. MMWR Morb Mortal Wkly Rep 2014;63:209-12.

SYPHILIS

DEFINITION

Syphilis is a systemic infection caused by *Treponema pallidum*. With the exception of mother-to-child transmission, syphilis is almost exclusively spread by direct contact with infectious lesions.

CLINICAL FEATURES

Stages Of Syphilis

A. Primary Syphilis

Usually occurs 2-6 weeks following infection. Characterized by a single or less often multiple, painless, indurated ulcer (chancre) at the site of inoculation. Regional lymph nodes are enlarged, feel rubbery and are painless.

B. Secondary Syphilis

Usually occurs 2-6 months following primary syphilis. Characterized by variable mucocutaneous and systemic signs e.g. symmetrical non-itchy rashes, mucous membrane lesions, patchy alopecia, generalised lymphadenopathy.

C. Latent Syphilis

Asymptomatic phase with no clinical signs of organ involvement.
It is categorised into:

- Early latent syphilis (<1 year of infection)
- Late latent syphilis (>1 year of infection)

D. Tertiary Syphilis

Occurs 5 to 10 years after secondary syphilis and includes:

- Benign tertiary syphilis characterized by gumma formation
- Cardiovascular syphilis
- Neurosyphilis

LABORATORY TESTS

Direct Detection Methods

T. pallidum cannot be cultured on routine laboratory culture media. Nucleic acid amplification testing (NAAT) for *T. pallidum* DNA is not commercially available. Dark-field microscopy remains the most common clinical test for direct detection of *T. pallidum.*

Dark-Field Microscopy

Dark-field microscopy (DFM) is particularly useful in early syphilis, when antibodies are not yet detectable. The diagnosis of syphilis may be confirmed by demonstrating *T. pallidum* on wet mounts of:

- Secretions from the primary chancre or
- Moist lesions of secondary syphilis

Serological Tests

Non-Treponemal Tests

The *Rapid Plasma Reagin (RPR)* test and the *Venereal Disease Research Laboratory (VDRL)* test are monitored serially to assess the serological response to treatment.

- RPR titres are slightly higher than VDRL titres.
- A positive RPR/VDRL test needs to be confirmed by a treponemal test.
- RPR/VDRL may become negative if treatment is instituted early in the disease. However, treatment of late infections often results in a persistently positive result, or a serological scar.
- A false-positive test may occur in HIV, autoimmune conditions, vaccinations, injecting drug use, pregnancy, and older age.

Treponemal Tests

The *Treponema Pallidum Haemagglutination Assay (TPHA)*, *Treponema Pallidum Particle Agglutination (TPPA)* test, the *Line Immunoassay (LIA)*, the *Fluorescent Treponemal Antibody Absorption (FTA-Abs*) test, Rapid diagnostic tests (e.g. *Abbott Determine Syphilis TP*) and the *treponemal EIA* test are specific and can be used as screening tests.

- A positive result may need to be confirmed by another specific test, as well as a non-treponemal test with a titre (e.g. RPR/VDRL).
- Once positive, specific tests tend to remain positive even after the syphilis has been successfully treated. The titres of treponemal tests are not useful in monitoring treatment response.

The FTA-Abs test is the first test to become positive following infection. It is followed by the RPR/VDRL test, and then by the TPHA/TPPA test. In primary syphilis, 85-90% of cases will have a reactive FTA-Abs test, but only 60% will have a reactive TPHA/TPPA. The FTA-Abs test is no longer routinely offered by laboratories in Singapore. The syphilis LIA test for both IgM and IgG can be done as an alternative confirmatory test, as well as to detect cases of early syphilis. There is evidence that the syphilis EIA test is also useful for detecting early infections.

Most cases of syphilis in HIV-infected persons will demonstrate typical serological responses. However, there may be instances of an altered serological response (abnormally high, low or fluctuating titres).

Testing for Neurosyphilis

Neurosyphilis is often difficult to diagnose, as there is no single test that is useful in all types of neurosyphilis.

Lumbar puncture is indicated for persons with neurological signs. It is not indicated for persons with isolated ocular or auditory abnormalities. Diagnosis of neurosyphilis depends on a combination of CSF tests (e.g., CSF cell count, protein, or reactive CSF-VDRL) in the presence of reactive serologic test (non-treponemal and treponemal) results and neurologic signs and symptoms.

CSF-VDRL is highly specific but insensitive. A positive CSF VDRL in the absence of gross blood contamination is confirmatory for neurosyphilis. However, there may be false negatives as the test is not very sensitive.

CSF FTA-Abs, CST-TPPA and CSF-LIA are less specific for neurosyphilis than the CSF-VDRL but is highly sensitive. Neurosyphilis is highly unlikely with a negative CSF FTA-ABS, or TPPA, or LIA test, especially among persons with non-specific neurologic signs and symptoms.

SN	Diagnosis	RPR / VDRL		TPHA / TPPA	EIA / TP Ab	LIA	
		Results	Titres			IgM	IgG
1	Pre-primary syphilis (Incubation period)	+/-	Rising	+/-	+/-	+/-	+/-
2	Primary syphilis	+/-	Rising	+/-	+/-	+/-	+/-
3	Secondary syphilis	+	High	+	+	+	+
4	Early latent syphilis Late latent syphilis	+ +/-	Mod Mod/Low	+ +	+ +	+/- -	+ +
5	CVS syphilis Neurosyphilis	+/- +/-	Mod/Low Mod/Low	+ +	+ +	- -	+ +
6	Early congenital syphilis	+	Rising	+	+	+/-*	+
7	Passive transfer of maternal antibodies	+	Same or lower than mother's	-	-	-	+
8	Late congenital syphilis	+	Mod/Low	+	+	-	+
9	Biological false positive reaction	+ -	Low NA	- -	- +	- -	- -
10	Treated early syphilis	-	NA	+/-	+/-	-	+/-
11	Treated late syphilis	+/-	Low	+/-	+	-	+

Table 1. Serological Responses in Syphilis
** LIA-IgM may be negative in feeble or premature infants*

TREATMENT
Parenteral penicillin G (aqueous crystalline, aqueous procaine, or benzathine) is the drug of choice for treating all stages of syphilis. If the patient is allergic to penicillin, tetracycline, doxycycline, azithromycin and erythromycin are the alternatives. However, they do not have the established and well-evaluated high rate of success of penicillin.

1. Early Syphilis

- Primary syphilis
- Secondary syphilis
- Early latent syphilis of less than 1 year duration

Recommended Regimen(s)

1. Benzathine Penicillin G 2.4 million units IM single dose **[III, B]**

or

2. Aq. Procaine Penicillin G 600,000 units IM daily x 10 days **[III, B]**

For patients allergic to penicillin:

1. Doxycycline 100mg orally BD x 14 days **[III, B]**

or

2. Tetracycline 500mg orally QDS x 14 days **[III, B]**

or

3. Erythromycin 500mg orally QDS x 14 days **[III, B]**

or

4. Azithromycin 500mg orally daily x 10 days **[IV, C]**

Note: For HIV-infected individuals, we recommend the same treatment regimens as those who are HIV negative (see section on infection in HIV-infected individuals). **[IV, C]**

2. Late Syphilis (excluding neurosyphilis)

- Latent syphilis of more than 1 year or unknown duration
- Late benign syphilis
- Cardiovascular syphilis

Recommended Regimen(s)

1. Benzathine penicillin G 2.4 million units IM weekly x 3 doses **[III, B]** (7.2 million units total)

or

2. Aq. Procaine penicillin G 600,000 units IM daily x 17-21 days **[III, B]**

Note: A maximum interval of 14 days between doses of Benzathine Penicillin might be acceptable for non-pregnant patients before restarting the sequence of injections. Ideally it should be 7-9 days.

For patients allergic to penicillin: (close follow-up required)

1. Doxycycline 100mg orally BD x 28 days [IV, C]

or

2. Tetracycline 500mg orally QDS x 28 days [IV, C]

or

3. Erythromycin 500mg orally QDS x 28 days [IV, C]

3. Neurosyphilis, Ocular and Otologic Syphilis

A high sustained blood level of penicillin is required for adequate penetration of the blood-brain barrier in the treatment of neurosyphilis.
Patients with syphilis should have a CSF examination if they have any of the following:

- Neurologic, cognitive, auditory or ophthalmic symptoms and signs
- Evidence of active tertiary syphilis (e.g. aortitis, gumma, iritis)
- Treatment failure

Some experts recommend CSF examination in HIV infection with late syphilis or syphilis of unknown duration (some experts would treat all HIV positive syphilis with neurosyphilis regimens) but newer evidence suggests that treatment outcomes are not significantly altered.

The CSF findings in neurosyphilis are:
- Increased mononuclear cell count (>5 cells/mm3)
- Increased total protein (>0.4 g/l)
- Positive CSF VDRL (negative in about 20%)
- Positive CSF LIA

Recommended Regimen(s)

1. Aq. Procaine penicillin G 2.4 million units IM daily x 10 days
   plus
   Probenecid 500mg orally QDS x 10 days

   followed by
   Benzathine penicillin G 2.4 mega units IM weekly x 3 doses **[III, B]**

or

2. Aq. Crystalline Benzyl penicillin 3 to 4 million units IV every 4 hours x 10 days
   (total 18 to 24 million units a day)

   followed by
   Benzathine Penicillin G 2.4 million units IM weekly x 3 doses **[III, B]**

For patients allergic to penicillin:
Penicillin is the drug of choice unless really contraindicated. RAST tests, skin testing and desensitisation should be performed in consultation with an expert.

Alternative Regimen(s)

1. Doxycycline 100mg orally BD x 28 days **[IV, C]**
   Preferred oral alternative in view of its more favourable dosing intervals

or

2. Tetracycline 500mg orally QDS x 28 days **[IV, C]**

or

3. Erythromycin base or stearate 500mg orally QDS x 28 days (least effective) **[IV, C]**

4. Oral Corticosteroid Cover

This is to minimize the effects of the Jarisch-Herxheimer reaction that may occur 4 to 12 hours after the first dose of antibiotic therapy.

Indications
It is indicated in the following situations where the reaction may result in morbidity or even mortality:
- Laryngeal gumma
- Cardiovascular syphilis
- Neurosyphilis

Recommended Regimen(s)

1. Prednisolone orally 20mg TDS (60mg/day) x 24 hours before treatment and continued x 2 days after starting therapy **[IV, C]**

FOLLOW-UP
Quantitative nontreponemal tests should be repeated for a total period of two years (at 3 months; 6 months; 12 months; 18 months; 24 months).

Following treatment of early syphilis, RPR/VDRL should demonstrate a 4x (2 dilutions) decrease in titre within 6 months. Failure to do so probably means treatment failure, and is an indication for retreatment with 3 injections of Benzathine penicillin. Some experts recommend CSF examination.

Clinical signs that persist or recur, or a rising RPR/VDRL titre of 4x or more suggests either reinfection or relapse. In these situations, CSF examination is recommended before retreatment. Seroreversion in primary syphilis often occurs within 12 months. It may take a longer time for secondary and early latent syphilis, but usually occurs within 24 months.

For latent syphilis non-treponemal tests should be repeated at 6, 12, and 24 months. Serologic response to treatment associated with multiple factors, viz. syphilis stage, initial non-treponemal titres (<1:8 are less likely to decline four-fold), and age (titres in older patients might be less likely to decrease fourfold than younger patients). These persons should be examined for HIV infection and neurologic disease, clinical and serologic follow-up annually. If additional follow-up cannot be ensured or if an initially high titre (>1:32) does not decrease at least four-fold 24 months after treatment, retreatment with weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks is recommended. Because treatment failure might be the result of unrecognised CNS infection, CSF examination can be considered in such situations where follow-up is uncertain or initial high titres do not decrease after 24 months.

Following treatment of late syphilis, seroreversion occurs rarely as a stable, low titre, serological scar, is the result in most patients.

All patients treated for neurosyphilis should be followed up for life at 6-month intervals. If CSF pleocytosis was present initially, CSF examinations should be repeated every 6 to 12 months until the cell count returns to normal. Serologic tests for HIV should be performed 3 months after the last risky exposure.

MANAGEMENT OF SEXUAL CONTACTS
At risk partners are those who have been exposed within the following periods: 3 months plus duration of symptoms for primary syphilis, 6 months plus duration of symptoms for secondary syphilis, and 1 year for early latent syphilis.

Epidemiologic treatment should be given to sexual contacts who were exposed 3 months prior to the diagnosis of primary, secondary or early latent syphilis, if follow-up is uncertain. Sexual partners of late syphilis should be screened and evaluated for syphilis, and treated on the basis of these findings.

Epidemiologic Treatment
Epidemiologic treatment can be given as follows:

1. Benzathine Penicillin G 2.4 million units IM single dose **[III, B]**

or

2. Doxycycline 100mg orally BD x 14 days **[III, B]**

or

3. Azithromycin 1g orally STAT **[III, B]**

CONSIDERATIONS IN PREGNANCY
All pregnant women should have serological tests for syphilis at the first antenatal visit. This should be repeated in women who have high-risk behaviour or have spouses who have high-risk behaviour.

Penicillin should be used in dosage schedules appropriate for the stage of syphilis as recommended for the treatment of non-pregnant patients. A Jarisch-Herxheimer reaction may precipitate premature labour or foetal distress. Women should be advised to seek obstetric care if abnormal contractions and decreased foetal movements occur.

For penicillin-allergic patients, give erythromycin in dosage schedules appropriate for the stage of syphilis as recommended for the treatment of non-pregnant patients. However, as erythromycin exhibits poor penetration across the placental barrier, the infant should be routinely treated with penicillin at birth. For these patients, retreatment with doxycycline can be considered after delivery when breastfeeding has been stopped.

1. Ceftriaxone 500mg IM daily x 10 days and Azithromycin 500mg orally daily x 10 days (limited data only) have been tried.

Tetracyclines are contraindicated in pregnancy. Pregnant woman treated for early syphilis should have monthly RPR/VDRL for the remainder of the current pregnancy.

CHILDREN WITH ACQUIRED SYPHILIS
Birth and maternal records should be reviewed to exclude congenital syphilis.

Primary, Secondary and Early Latent Syphilis
1. Benzathine penicillin G 50,000 units/kg IM, up to adult dose of 2.4 mega units in single dose.

Late latent syphilis, latent syphilis of unknown duration, late syphilis (not neurosyphilis)
1. Benzathine penicillin G 50,000 units/kg IM, up to adult dose of 2.4 mega units, administered as three doses at 7 days intervals (total 150,000 units/kg up to adult dose of 7.2 million units)

Neurosyphilis
1. Aq. Crystalline Penicillin G 50,000 unit/kg IV every 4-6 hours (total 200,000-300,000 unit/kg/day) x 10 days.

CONGENITAL SYPHILIS
Diagnosis and treatment decisions must be based on:
- Identification of syphilis in the mother
- Adequacy of maternal treatment
- Clinical, laboratory, radiological evidence of syphilis in the infant
- Comparison of the infant's RPR/VDRL result with the mother's

Who should be evaluated?
Infants should be evaluated if they have been born to seropositive mothers who
- have untreated syphilis
- were treated for syphilis <1 month before delivery
- were treated for syphilis during pregnancy with a non-penicillin regimen
- did not have the expected decrease in non-treponemal antibody (RPR or VDRL) titres after treatment for syphilis
- were treated but had insufficient serologic follow-up during pregnancy to assess disease activity

Evaluation is not required if both these criteria are met:
- Mother had well-documented history of treatment in pregnancy with a penicillin regimen appropriate for the stage of syphilis
- Mother has sufficient serologic follow-up after treatment to show that she responded to treatment (≥4-fold decrease in RPR/VDRL titre in early syphilis; stable or declining titres of ≤1:4 in other patients)

Note: Some experts would treat the infant with a single dose of Benzathine Penicillin 50,000 units/ kg IM; others would not but instead provide close serologic follow-up. If the infant's RPR/ VDRL is non-reactive no treatment is needed

What to evaluate in the infant?

- Thorough physical examination
- Infants blood: RPR/VDRL, LIA IgM or EIA IgM on the serum if available
- DG or DIF microscopy of suspicious lesions or body fluids
- CSF: FEME, VDRL, LIA IgM
- Other tests as clinically indicated (e.g. long bone and chest X-rays, FBC)

When to treat infants?

- Positive syphilis serology with evidence of active disease (physical examination or X-ray): rhinitis, mucocutaneous signs, hepatosplenomegaly, osteitis, periostitis, osteochondritis, glomerulonephritis, ascites, stigmata)
- A reactive CSF-VDRL
- An abnormal CSF finding (WBC >5/mm or protein >50mg/ml) regardless of CSF VDRL titre
- A detectable LIA IgM in the infant
- VDRL titre in the infant is fourfold or greater than in the mother
- VDRL titres in the infant show a serial rise
- Treatment of the mother was inadequate or unknown (adequate maternal treatment means full dosage of penicillin at least 1 month before delivery)
- Drugs other than penicillin e.g. erythromycin was used to treat the mother during pregnancy

Recommended Regimen(s)

1. Aq. Crystalline Penicillin G 50,000 units/kg/day IV daily every 12 hours (total 100,000 to 150,000 units/kg/day) during the first 7 days of life, and every 8 hours thereafter for a total of 10 days **[III, B]**

   or

2. Aq. Procaine Penicillin G 50,000 units/kg IM daily single dose x 10 days **[III, B]**

   or

3. Benzathine penicillin 50,000 units IM single dose may be used if the infant's evaluation is normal and follow-up is certain. However, if any part of the evaluation is abnormal, not done or cannot be interpreted, a 10 day course of penicillin is needed **[IV, C]**

Follow-up for Seroreactive Infants

Seroreactive infants and infants whose mothers were reactive at delivery should be followed up every 2-3 months until the test becomes nonreactive or the titre falls fourfold; the RPR/VDRL should fall by 3 months of age and be nonreactive by 6 months of age if the infant was not infected (passive transfer) or if treatment was adequate. Treatment after the neonatal period may result in a slower decline of titres.

Passively transferred treponemal antibodies may be present in the infant for 15 months, the presence of a reactive treponemal test after 18 months indicates congenital syphilis, and the infant should be (re)evaluated.

Congenital Syphilis in Older Infants and Children

- Review maternal serology and records if congenital syphilis is possible
- Full evaluation including CSF examination, eye and auditory examination, X-rays etc

Recommended Regimen(s)

1. Aq. crystalline penicillin G 200,000-300,000 units/kg/day IV (administered as 50,000 units/kg every 4-6 hours) x 10 days **[IV, C]**

or

2. Aq. Procaine Penicillin G 50,000 units/kg IM daily single dose x 10 days **[IV, C]**

CONSIDERATIONS IN HIV INFECTION

Serological tests for syphilis are generally reliable in HIV co-infection. Some authorities recommend routine CSF examination and/or treatment for neurosyphilis for all patients, regardless of the stage of syphilis. However, most HIV-infected persons respond appropriately to standard benzathine penicillin for primary and secondary syphilis. CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) are common in HIV-infected persons, even in those without neurologic symptoms, although the clinical and prognostic significance of such CSF abnormalities with primary and secondary syphilis is unknown. Several studies have demonstrated that among persons infected with both HIV and syphilis, clinical and CSF abnormalities consistent with neurosyphilis are associated with a CD4 count of ≤350 cells/mL and/or an RPR titre of ≥1:32; however, unless neurologic symptoms are present, CSF examination in this setting has not been associated with improved clinical outcomes.

A lumbar puncture is recommended for HIV patients with syphilis if there are any neurological abnormalities, or if titres do not decline after penicillin therapy. All HIV patients should be treated wherever possible with penicillin.

Some experts recommend treatment in the same doses as for HIV negative patients, while others would treat all HIV-infected patients with the neurosyphilis regimen. **[IV, C]**

We recommend that all HIV-infected patients without evidence of neurosyphilis be given doses of benzathine penicillin that are appropriate for the stage of syphilis as in non-HIV infected patients.

However, it is more important to monitor for treatment failures in these patients. Such patients should be followed-up clinically and with nontreponemal tests at 3, 6, 9, 12 and 24 months after treatment.

RE-TREATMENT

Consider referral to infectious disease specialist. Indications for referrals include:

- Clinical signs and symptoms of syphilis persist or recur (clinical relapse)
- Four-fold or greater rise in RPR/VDRL titre e.g. from R4 to R16 (serological relapse)
- Initial high RPR/VDRL titre e.g. R32 or greater persists for a year (sero-fast)
- Failure of RPR/VDRL titre to decrease four-fold after a year for treated early syphilis
- For pregnant women treated for early syphilis, the failure to show a four-fold decrease in RPR/VDRL titre after 3 months.

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. BASHH.(2015). UK National Guidelines on Management of Syphilis. (updated July 2019)

TRICHOMONIASIS

DEFINITION

Trichomoniasis is a sexually transmitted infection (STI) of the genital tract caused by the protozoan *Trichomonas vaginalis* (TV). Women are the main carriers of the disease; men who are infected men are usually asymptomatic.

CLINICAL FEATURES

Vaginal trichomoniasis may be asymptomatic (up to 50%) or cause abnormal vaginal discharge (the classical frothy yellow-green discharge occurs in 10-30%), vulval itching, dysuria, or offensive odour. Other signs include vulvitis, vaginitis and 2% of patients have strawberry cervix. Up to 50% of men with *T. vaginalis* are asymptomatic and usually present as sexual partners of infected women. Some male patients may have symptoms of urethritis and rarely balanoposthitis.

Complications

T. vaginalis infection in pregnant women is associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and delivery of a low birthweight infant. *T. vaginalis* infection at delivery may predispose to maternal postpartum sepsis.

LABORATORY TESTS

- Light-field microscopy of a wet mount of vaginal secretions (taken from the posterior fornix) mixed with normal saline will show trichomonads, about the size of white blood cells moving with a jerky motion (sensitivity 60-70%). The wet preparation should be read within 10 min of collection, as the trichomonads quickly loose motility and may be more difficult to identify. This is not a sensitive test in men.
- Culture has a higher sensitivity (75-96%) compared to microscopy and can detect *T. vaginalis* in men.
- Nucleic acid amplification tests (NAATs) offer the highest sensitivity for the detection of *T. vaginalis* and should be the test of choice where available.
- Point-of-care test e.g. OSOM Trichomonas Rapid Test (Genzyme Diagnostics, USA) has demonstrated a high sensitivity and specificity.
- Trichomonads are sometimes reported on cervical cytology (sensitivity ~ 60-80%) but there is a high false-positive rate of about 30%. Use of liquid-based PAP smear testing has shown enhanced sensitivity. The diagnosis should still be confirmed by direct microscopy of vaginal secretions or culture.
- All women should be screened for other STIs and HIV.

TREATMENT

Both symptomatic and asymptomatic patients should be treated.

Recommended Regimen(s)

Adults

1. Metronidazole 400-500mg orally BD x 7 days **[Ib, A]**

or

2. Metronidazole 2g orally single dose **[Ib, A]**

or

3. Tinidazole 2g orally single dose

Allergy to metronidazole

There is no effective alternative to nitroimidazole compounds. Patients with an IgE mediated-type allergy to a nitroimidazole can be managed by metronidazole desensitization.

Note: Metronidazole gel is not recommended because it is less efficacious (<50%). Metronidazole and tinidazole may provoke a disulfiram-like reaction when taken with alcohol. Patients should be advised to abstain from alcohol use during treatment and for 24 hours after completion of metronidazole (72 hours after completion of tinidazole).

Children

T. vaginalis infection may be acquired perinatally and occurs in ~5% of babies born to infected mothers. Infection beyond the first year of life should suggest sexual contact and the child should be appropriately evaluated.

1. Metronidazole 15mg/kg orally TDS x 7 days

CONSIDERATIONS IN PREGNANCY

T. vaginalis infection has been associated with adverse pregnancy outcomes; all infected pregnant women should be treated. Metronidazole in pregnancy has not been shown to be teratogenic or mutagenic and can be used during all stages of pregnancy or breastfeeding. Imidazole and metronidazole pessaries may be used to provide symptomatic relief, but oral metronidazole is needed for eradication of infection.

Metronidazole is secreted in breast milk and may affect its taste. Avoid high doses if breastfeeding or if using a single dose of metronidazole, breastfeeding should be discontinued for 12-24 hours to reduce infant exposure.

CONSIDERATIONS IN HIV INFECTION

T. vaginalis infection in HIV-infected women has been shown to enhance HIV transmission by increasing genital viral shedding. Treatment of TV has been shown to reduce HIV shedding. Rescreening at 3 months after completion of therapy should be considered in HIV-positive women.

1. Metronidazole 400mg orally BD x 7 days should be used
   Single dose metronidazole is not as effective in women with HIV.

PERSISTENT SYMPTOMS

Patients with persistent symptoms treated with either regimen should be retreated.

1. Metronidazole 400mg orally BD x 7 days

If treatment failure occurs again (and reinfection, non-compliance excluded), treat with:

1. Metronidazole 2g orally daily x 5-7 days

Failure after the third regimen should prompt antibiotic resistance testing.

FOLLOW UP

Follow-up is unnecessary for asymptomatic patients.

MANAGEMENT OF SEXUAL CONTACTS

Sex partners within 4 weeks prior to presentation of symptoms (or last sexual partner if >4 weeks) should be treated on epidemiological grounds and screened for other STIs. They should be advised to abstain from intercourse until they and their sex partners have been adequately treated and any symptoms have resolved. There is evidence to suggest that patient-delivered partner therapy might have a role in partner management for trichomoniasis.

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. BASHH (2014). National Guideline for the Management of Trichomonas Vaginalis Infection.

VACCINATIONS TO PREVENT POTENTIAL STIs

INTRODUCTION
Immunisations are important in the prevention of human papillomavirus (HPV), hepatitis A and hepatitis B (refer to respective chapters on HPV & hepatitis).

1. HUMAN PAPILLOMAVIRUS (HPV)
HPV vaccination provides safe, effective and lasting protection against the HPV infections that most commonly cause cancer. HPV-related cancers include cancer of the oropharynx, cervix, vulva, vagina, penis, anus.

Three HPV vaccines are available for the prevention of HPV infection:
1. A bivalent vaccine (Cervarix), which protects against HPV types 16 and 18 and
2. A quadrivalent vaccine (Gardasil-4), which protects against types 6, 11, 16 and 18.
3. A 9-valent vaccine (Gardasil-9), which protects against type 6, 11, 16, 18, 31, 33, 45, 52 and 58.

Both Cervarix and Gardasil-4 vaccines offer protection against the HPV types that cause up to 70% of cervical cancers (types 16 and 18) and the quadrivalent HPV vaccine has additional protection against HPV types that are commonly associated with genital warts (types 6 and 11).

The Gardasil-9 vaccine offers protection against HPV types up to 95% of cervical cancers and 90% of genital warts.

Recommendations
As of August 2019, CDC Atlanta has provided the following recommendations:
- Female & male children and adults aged 9 through 26 years to receive the HPV vaccination.
- The vaccination is to be routinely recommended at age 11 or 12 years.
- The vaccination can be given starting at age 9 years.
- Catch-up HPV vaccination is also recommended for all persons through age 26 years who are not adequately vaccinated.
- For female & male adults aged >26 years, catch-up vaccination is not recommended. Instead, shared clinical decision making regarding HPV vaccination is recommended for some adults aged 27 through 45 years who are not adequately vaccinated.
- HPV vaccines are not licensed for used in adults aged >45 years.
- Vaccination is recommended and may be beneficial for gay/bisexual MSM, transgender persons, and certain immunocompromised individuals.
- The Advisory Committee on Immunization Practices (ACIP) does not recommend serologic or HPV DNA testing prior to immunisation.
- For maximum benefit, the HPV vaccination should be administered before onset of sexual activity since neither vaccine treats or accelerates the clearance of pre-existing vaccine-type HPV infections or related disease. However, a history of an abnormal Papanicolaou smear, genital warts, or HPV infection is NOT a contraindication to HPV immunisation.

Vaccination Schedule
If the first dose of HPV vaccine is given before the 15th birthday, vaccination should be given according to the 2-dose schedule: the second dose is recommended 6-12 months after the first dose.

Adolescents who received their two doses less than five months apart will require a third dose of HPV vaccine.

If the first dose of any HPV vaccine is given on and after the 15th birthday, vaccination should be completed according to a 3-dose schedule: the second dose is recommended 1-2 months (minimum 4 weeks) after the first dose, and the third dose is recommended 6 months after the first dose. (Minimum 12 weeks between second and third dose, 5 months between first and third dose)

Although minimum intervals are stated, there is no maximum interval. There is no reason to restart the vaccine series if the HPV vaccine schedule is interrupted. Patients, who have exceeded the minimum interval for the next dose by months or even years, may be given the next dose needed.

HPV vaccine is not recommended for use in pregnancy. Women who become pregnant before completing the vaccination schedule should defer the subsequent doses until the pregnancy is completed. There is no need to restart the entire vaccination schedule but there should not be a delay of more than 12 months between the second and third dose.

Lactating women can be vaccinated. The HPV vaccine is an inactivated vaccine which does not contain a whole virion, hence it does not affect the safety of breastfeeding for mothers or infants
Women who have received the HPV vaccine should continue routine cervical cancer screening because 30% of cervical cancers are caused by HPV types other than 16 or 18, and even with Gardasil-9 vaccine, the protection against cervical cancer is not 100%. Cervical cancer screening can be in the form of Papanicolaou smear or HPV testing, depending on the centre's practice.

2. HEPATITIS B

Risk factors associated with hepatitis B virus (HBV) infection are unprotected sex with an infected partner, unprotected sex with more than one partner, and a history of other STIs. MSM and intravenous drug users (IVDU) are considered at risk groups for HBV acquisition. HBV is also endemic in Southeast Asia therefore vaccination is recommended for the general population.

The ACIP recommends universal hepatitis B immunisation for all unvaccinated adults presenting to a STI clinic. Patients with a history of HBV vaccination should have either documentation of immunisation or serologic testing for hepatitis B surface antibody. Please refer to the chapter on viral hepatitis for the appropriate screening tests and the vaccine administration schedule.

All pregnant women receiving STI services should be tested for HBsAg, regardless of whether they have been previously tested or vaccinated.

All HIV-infected patients should receive HBV immunisation. Although the vaccine is safe, efficacy can be affected by the presence of HIV RNA and advanced immunosuppression.

3. HEPATITIS A

Vaccination against hepatitis A is recommended by the CDC for MSM, IVDU and patients with chronic liver disease. Post vaccination serologic testing is not recommended because most persons respond to the vaccine.

Hepatitis A virus replicates in the liver and is shed in high concentrations in faeces from 2 weeks before to 1 week after the onset of clinical illness. Since sexual transmission of hepatitis A probably occurs because of faecal-oral contact, barrier measures, such as condoms, are ineffective in preventing acquisition of this disease.

Immunization is also recommended for HIV-infected patients who have chronic liver disease or are at risk for hepatitis A (such as MSM, IVDU). Hepatitis A vaccine is safe and effective in HIV-infected patients, particularly when administered before an onset of advanced immunosuppression.

SUMMARY OF VACCINATIONS

Type of vaccination	Dose 1	Dose 2	Dose 3
HPV vaccine	Day 1	Month 1-2	Month 6
Hepatitis B	Day 1	Month 1	Month 6
Hepatitis A	Day 1	Month 6	Not applicable

References:

1. Workowski, KA. et al. CDC Atlanta MMWR Sexually Transmitted Infections Treatment Guidelines 2021. Volume 70, no 5. July 2021

2. Centers for Disease Control and Prevention MMWR 16 Aug 2019. Human Papillomavirus Vaccination schedules and recommendations.

VIRAL HEPATITIS

HEPATITIS A VIRUS

DEFINITION

Hepatitis A (HAV) is an RNA virus in the family *Picornaviridae*. Transmission occurs via faeco-oral (via food, water, close personal contact) route. Outbreaks have been reported in MSM, linked to oro-anal or digital rectal contact. Outbreaks have also been reported amongst intravenous drug users, in institutions for people with learning difficulties, and in contaminated batches of factor VIII.

Patients are infectious for approximately 2 weeks before and 1 week after the jaundice by the non-parenteral routes but virus can be found in the blood and stool until after the serum amino transferase levels have peaked. In HIV positive patients, HAV viraemia may continue for over 90 days.

In 2017, there were 81 serologically confirmed HAV infections in Singapore.

CLINICAL FEATURES

Incubation Period: 15-45 days
Most children and up to half of adults are asymptomatic or have mild non-specific symptoms with little or no jaundice.

In the more 'typical' case there are 2 phases of symptoms

- The prodromal illness: flu-like symptoms (malaise, myalgia, fatigue), often with right upper abdominal pain. This phase lasts for 3-10 days.
- This is followed by the icteric illness: jaundice (hepatic and cholestatic) associated with anorexia, nausea, fatigue, liver enlargement and tenderness. Usually lasts for 1- 3 weeks. It can persist for 12 or more weeks in a minority of patients who have cholestatic symptoms (itching and deep jaundice).

Fulminant hepatitis complicates approximately 0.4% of cases, and is more common in patients who are already infected with chronic hepatitis B or C. Chronic infection (>6 months) has only been reported in a very small number of case-reports; overall mortality is <0.1%.

DIAGNOSIS

Confirmed by a positive serum Hepatitis A virus specific IgM (HAV-IgM) which remains positive for six months or more.

HAV-IgG does not distinguish between current or past infection and may remain positive for life. Antibody produced in response to HAV infection persists for life and confers protection against reinfection.

<u>Other Tests</u>

- Serum amino-transferases (AST/ALT)
- Bilirubin

ALP will usually be <2x the upper limit of normal, but higher if there is cholestasis. PT prolongation by more than 5 seconds suggests developing hepatic decompensation.

TREATMENT

Patients should be advised to avoid food handling and unprotected sexual intercourse until they have become non-infectious.

Hepatitis A is a notifiable disease. Screen for other STIs in cases of sexually-acquired hepatitis or if otherwise appropriate.

<u>Mild/Moderate Icteric Hepatitis (80%)</u>
Manage as an outpatient emphasising rest and oral hydration

Severe Icteric Hepatitis
For patients with vomiting, dehydration or signs of hepatic decompensation (change in conscious level or personality), consider admission to hospital.

MANAGEMENT OF SEXUAL CONTACTS
Partner notification should be performed for at-risk homosexual contacts (oral/anal, digital/rectal and penetrative anal sex) within the period 2 weeks before to 1 week after the onset of jaundice.

Hepatitis A single-antigen vaccine may be given up to 14 days after exposure providing exposure was within the infectious period of the source case (during the prodromal illness or first week of jaundice). **[IIa, B]**

Hepatitis A vaccine schedule: doses at 0 and 6-12 months, 95% protection for at least 5 years. **[Ib, A]**

There is increasing evidence that vaccine-induced immunity may be >20 years and possibly lifelong, so no further booster doses is currently recommended after the primary course in immunocompetent patients.

HIV positive patients respond in 46-88% but titres are lower than in HIV negative individuals, and correlates with CD4 count. **[IIa, B]**

A combined Hepatitis A+B vaccine given on the same schedule as the hepatitis B vaccine has similar efficacy to the individual vaccines although early immunity to hepatitis B may be impaired. **[IIa, B]**

PRIMARY PREVENTION
Most MSM are not at increased risk for hepatitis A infection and therefore universal vaccination in this group cannot be firmly recommended. **[III, B]** However, many outbreaks have been reported amongst homosexual men in large cities and therefore clinics in these areas should offer vaccination, particularly when increased rates of infection have been recognised locally. **[III, B]**

Screening for pre-existing hepatitis A exposure before vaccination has been found to be cost effective. **[III, B]**

Intravenous drug users and patients with chronic hepatitis C infection should be vaccinated. **[III, B]** Vaccination is also recommended for travellers to developing countries, people with haemophilia or chronic liver disease, those with occupational exposure and for people at risk in an outbreak. **[Ib, A]** Post-vaccination serologic testing is not indicated because most persons respond to the vaccine.

HEPATITIS B VIRUS

DEFINITIONS
Hepatitis B virus (HBV) is a DNA virus belonging to the *Hepadnavirus* family and is transmitted from person-to-person via blood or body fluids. Recognized modes of transmission include mother-to-child transmission, blood transfusion, nosocomial infection, sharing of needles and sexual transmission.

The predominant mode of transmission of HBV depends on the prevalence. Mother-to-child transmission is the major route of transmission in high-prevalence areas, while injection drug abuse and unprotected sexual intercourse are the predominant mode of transmission in low prevalence countries.

HBV universal vaccination was introduced in Singapore on 1 Sep 1987. The prevalence of HBsAg among children and adolescents aged 5-17 years was 0.4% in a seroprevalence study conducted between 2008 and 2010. The overall HBsAg prevalence among Singapore residents aged 18-69 years was 3.6% in 2010, corresponding to an intermediate prevalence area as defined by WHO.

Acute hepatitis B infection is a legally notifiable disease. In 2017, a total of 38 acute hepatitis B infections were reported.

ACUTE HEPATITIS B INFECTION

Incubation period: 1 to 4 months

In adults, approximately 70% with acute HBV infection are asymptomatic. The remaining 30% may experience a prodromal serum-sickness-like phase followed by constitutional symptoms such as jaundice, nausea, malaise and right upper quadrant pain.

Fulminant hepatic failure is uncommon, occurring in about 0.1 to 0.5% of patients. There is increased risk of fulminant or more severe hepatitis in patients who are co-infected with other hepatitis viruses and HIV, took acetaminophen during the illness or who are drug abusers, especially methamphetamine.

Neonates with HBV infection rarely show clinical features or transaminitis at birth. A small number develop acute hepatitis by 2 months of age, presenting with jaundice and elevated liver enzymes.

CHRONIC HEPATITIS B INFECTION

The age of infection largely determines the risk of progression from acute to chronic HBV infection. Perinatally acquired HBV has 90% chance of progressing to chronic HBV infection. This drops to 20-50% for infections acquired between 1 to 5 years old and less than 5% in adult acquired HBV infection.

Except those with decompensated liver cirrhosis, many patients with chronic HBV infection are asymptomatic. Furthermore, only in a small percentage is a known history of acute hepatitis elicited. Some patients may have non-specific symptoms such as malaise. Stigmata of chronic disease and extra-hepatic manifestations of HBV may be found on clinical examination.

LABORATORY TESTS

The order of appearance of markers in acute infections is HBsAg, HBeAg, anti-HBc IgM, anti-HBe, anti-HBc IgG, anti-HBs.

The significance of HBs antigen and antibody markers is shown below in Table 1.

HBsAg	Presence of HBV
HBeAg	Virus replication, high infectivity
Anti-HBc IgM	Acute infection
Anti-HBc IgG	Late acute, chronic, or previous infection
Anti-HBe	Loss of replication, low infectivity
Anti-HBs	Protective antibody

Table 1. Markers of Clinical Significance

TREATMENT

Treatment should normally be given in collaboration with a hepatologist or physician experienced in the management of liver disease.

Patients should be advised to avoid unprotected sexual intercourse until they have become non-infectious or their partners have been successfully vaccinated.

Hepatitis B is a notifiable disease. Screen for other STIs in cases thought to have been sexually acquired or if otherwise appropriate.

General Counselling

- No donation of blood, sperm, milk, organs
- No sharing of toothbrushes, shavers
- Household contacts, sexual partners to be immunized if negative HBsAg, anti-HBs and anti-HBc
- Pregnant carrier: inform O&G
- Healthy diet
- Avoid regular alcohol
- Steroids and immunosuppressive agents can aggravate latent infection.
- Clean blood spills with bleach/detergents

Note: Hepatitis B virus transmission is not transmissible through:

- Sharing of utensils, food or kissing as part of social greetings
- Participating in all activities including contact sports and social interaction with others (e.g. in schools, day care centres)

Acute Hepatitis B Infection

Acute HBV infection is diagnosed when HBsAg and anti-HBc IgM is detected. For most patients with acute HBV infection, treatment is mainly supportive. In immunocompetent adults, less than 1% develop liver failure, while less than 5% progress to chronic HBV infection.

In patients with severe liver disease such as those with coagulopathy, marked jaundice or with persistent symptoms, tenofovir or entecavir can be used as monotherapy until the patient has cleared HBsAg (2 tests done 4 weeks apart).

Chronic Hepatitis B Infection

Chronic HBV infection is based on the presence of HBsAg for longer than six months. Indications for treatment depends on the presence of liver inflammation, HBV viral load, antibody response, and risk factors for progression. Refer to table for indications for treatment in patients without cirrhosis.

HBeAg	HBV DNA (units/ml)	ALT	Treatment
-	>2000	>2x ULN	Indicated
-	≤2000	Within ULN	Monitor and treat if HBV DNA and ALT increase as described above
+	>20,000	>2x ULN	Treatment indicated in liver decompensation. Otherwise observe for 3 to 6 months and treat if no spontaneous HBeAg loss.
+	>20,000	≤2x ULN	Monitor patient and start treatment if ALT elevated to 2x ULN or if there is evidence of liver fibrosis

Table 2. Recommendations for Starting Treatment in Chronic HBV Patients without Cirrhosis and Not Pregnant

For patients with compensated cirrhosis, treatment with antivirals should be started irrespective of HBeAg status or ALT levels and should be considered even if HBV DNA is not detectable. Liver transplant can be an option for decompensated cirrhosis.

Choice of Antiviral Agents

Pegylated Interferon alfa-2a

Associated with more side effects than other agents, some of which can be severe. Advantage of offering a finite duration of treatment in young immunocompetent patients with well compensated liver disease.

Entecavir

Entecavir is a potent antiviral agent with low rate of drug resistance in treatment naïve patients. However, it should be avoided in lamivudine-resistant disease because of the high rates of development of entecavir resistance in such patients.

Tenofovir

Tenofovir is considered a first-line treatment both in treatment-naïve patients and in those with prior exposure or resistant to other nucleotide analogues like lamivudine.

Lamivudine

Despite its low cost and long history of safety, lamivudine is used less often now because of other effective treatment and the high rates of resistance.

Telbivudine
Not recommended because of the increased risk of resistance and adverse effects such as myopathy and peripheral neuropathy

Adefovir
Adefovir used to be an important adjunct in the treatment of lamivudine-resistant HBV, but this role has been replaced by newer agents like tenofovir.

MONITORING THERAPY
Besides checking for drug-related adverse effects, the following monitoring should be done for patients on treatment:

- HBV DNA every 3 months till undetectable for 2 consecutive visits, then monitor every 6 months
- Transaminases every 3 months
- HBeAg, anti-HBe every six months if initially positive
- HBsAg every year

SCREENING FOR HEPATOCELLULAR CARCINOMA
Regular active screening for hepatocellular carcinoma with ultrasound as frequently as every 6 months is recommended.

HEPATITIS B AND HIV

- Prior to starting HBV treatment, HIV tests should be performed.
- Tenofovir and lamivudine should only be given as part of a 3 drug anti-retroviral regimen for HIV treatment.
- Entecavir should not be used in patients with HIV not adequately suppressed as it causes the M184V (lamivudine/emtricitabine) resistant mutation.

CONSIDERATIONS IN PREGNANCY, BREASTFEEDING
The risk of vertical transmission of HBV from HBsAg positive mothers is as high as 90% in women who are HBeAg positive. This risk is about 30% in HBeAg negative mothers.

New-borns of mothers who test positive for HBsAg should receive both passive and active immunization (using Hepatitis B specific immunoglobulin) within 12 hours of delivery at different sites. Infants should go on to complete the whole HBV immunization series. Even with passive-active immunization, children born to HBeAg positive mothers remained at risk of transmission (about 9%).

Infants who received HBV active-passive immunization at birth can be breastfed. The infant should complete the hepatitis B vaccine series. However, for mothers who require antiviral treatment, the safety of antiviral therapy during breastfeeding is currently unclear.

MANAGEMENT OF SEXUAL CONTACTS
Partner notification should be performed and documented and the outcome documented at the subsequent follow-up. Contact tracing should include any sexual contact or needle-sharing partners during the period in which the index case is thought to have been infectious.

The infectious period is from 2 weeks before the onset of jaundice until the patient becomes surface antigen negative. In cases of chronic infection trace contacts as far back as any episode of jaundice or to the time when the infection is thought to have been acquired, this may be impractical for periods of longer than 2 or 3 years.

SCREENING AND PRIMARY PREVENTION
Hepatitis B testing in asymptomatic patients should be considered in MSM, sex workers, injecting drug users, HIV-positive patients, sexual assault victims, needle-stick victims and sexual partners of positive or high-risk patients. If non-immune, consider vaccination. If found to be chronic carriers, consider referral for therapy.

With the exception of new-borns, serological screening provides a basis for vaccination of an individual without giving an infected individual a false sense of security. Prophylactic vaccination is of no benefit to an individual who already has chronic hepatitis B virus infection; he/she should instead be followed

up regularly and treated when indicated. Serological screening for HBsAg and Ab should be done within 6 months' pre-vaccination for all except new-born babies.

Based on the results of an individual's serological screening for HBs Ag and Ab, clinicians should act according to the table below.

HBsAg	Anti-HBs	Interpretation	Action to take
Non-reactive	<10 IU/L	*Did not have* hepatitis B vaccination before: Not immune to hepatitis B Virus	Administer hepatitis B vaccination
		Had hepatitis B vaccination before Either: • The antibody level has waned to less than 10 IU/L, but the individual is still immune to the hepatitis B virus. or • The individual did not develop immunity against hepatitis B virus after the primary course of hepatitis B vaccination.	Offer a booster dose of hepatitis B vaccination and check anti-HBs within 3 months or Give them another course (3 injections) of hepatitis B vaccination & recheck anti-HBs within 3 months. Discuss options with patient.
Non-Reactive	> 10 IU/L	Immune to hepatitis B	Immunisation is not required
Reactive	<10 IU/L	Presence of hepatitis B virus infection	Clinically assess the patient for liver disease. To repeat the HBsAg test 6 months later. If HBsAg positive 2 times, 6 months apart, chronic hepatitis B infection confirmed.

Table 3. Interpretation of Hepatitis B Serology

For individuals previously vaccinated and with anti-HBs levels <10 IU/L, consider repeat booster of HBV vaccination or give a second course of HBV vaccination before rechecking the anti-HBs antibody titre. **[II, C]**

For immuno-competent people:
- With low risk of acquiring HBV and
- Who have completed their HB vaccination and
- Who had previously demonstrated immunity to HBV after vaccination

There is no need to check for immunity again or receive booster injections if their anti-HBs is <10 IU/L later on. **[II, C]**

Anti-HBc (total) should be checked if an otherwise immunocompetent individual fails to seroconvert after 2 courses of HBV vaccinations.

1. HBsAg negative, anti-HBs <10 IU/L, anti-HBc positive: These individuals may have HBV infection with low viral load and an undetectable level of HBsAg. Refer to specialists for further workup.
2. HBsAg negative, anti-HBs <10 IU/L, anti-HBc negative: Consider repeat vaccination with pre-S vaccine or other 3rd generation vaccine, if available, especially if the individuals belong to

the high-risk group. They should be advised against high risk behaviour, which may expose them to Hepatitis B infections, and counselled about PEP with HBIG if they do sustain high risk exposure. **[III, D]**

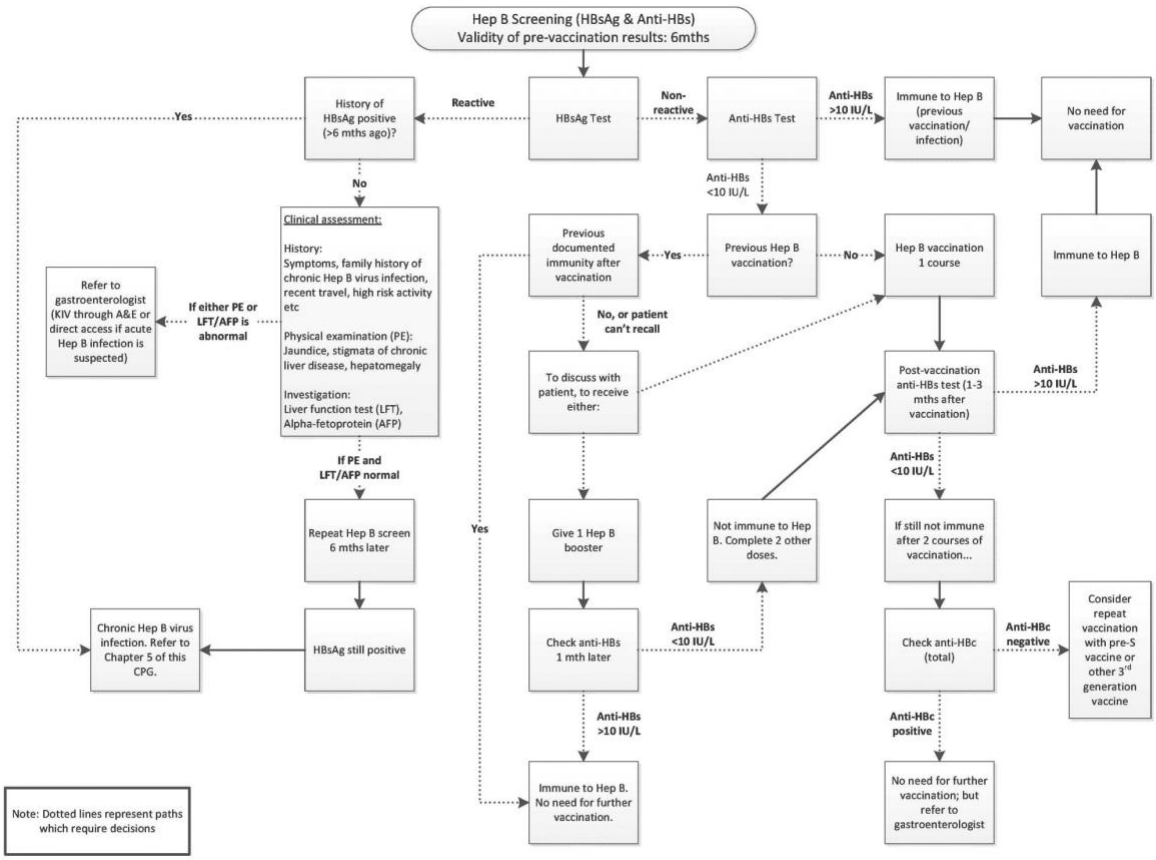


Figure 1. Algorithm for Hepatitis B screening & vaccination

POST VACCINATION TESTING FOR SEROLOGIC RESPONSE

Serologic testing for immunity is not necessary after routine vaccination of adolescents or adults. Testing 1-2 months after vaccination is recommended for persons whose subsequent clinical management depends on knowledge of their immune status e.g. health-care workers, HIV-infected persons and other immunocompromised persons, to determine the need for revaccination and the type of follow-up testing; and sex and needle-sharing partners of HBsAg positive persons to determine the need for revaccination and for other methods to protect themselves from HBV infection.

Persons determined to have anti-HBs levels of <10mIU/mL after the primary vaccine series should be revaccinated with a 3-dose series, followed by anti-HBs testing 1-2 months after the third dose. Patients who fail to respond after three additional doses of vaccine that have been administered properly are unlikely to benefit from further vaccination. Such patients should receive counselling on how to prevent HBV infection and the use of HBIG as post-exposure prophylaxis in the event of sexual or parenteral exposure to a person who is HBsAg positive.

POST EXPOSURE PROPHYLAXIS (PEP)

- Specific hepatitis B immunoglobulin intramuscularly (HBIG) may be administered to a nonimmune contact after a single unprotected sexual exposure or parenteral exposure/needle stick injury if the donor is known to be infectious. This works best within 48 hours and is of no use after more than seven days **[Ib, A]**
- An accelerated course of recombinant vaccine should be offered to those given HBIG plus all sexual and household contacts (at 0, 7 and 21 days or 0, 1, 2 months with a booster at 12 months in either course). **[Ib, A]** Vaccination theoretically will provide some protection from disease when started up to six weeks after exposure

- Avoid sexual contact, especially unprotected penetrative sex, until vaccination has been successful (anti-HBs titres >10IU/L.)

HEPATITIS C VIRUS

DEFINITION
Hepatitis C is a RNA virus in the *Flaviviridae* family.

Parenteral spread accounts for the majority of cases through shared needles/syringes in IDUs, transfusion of blood or blood products (pre-1990s), renal dialysis, needle-stick injury or sharing a razor with an infected individual.

Sexual transmission occurs at a low rate (generally <1% per year of relationship, or about 2% of spouses in long term relationships) but these rates increase if the index patient is also infected with HIV. There has been a steadily rising incidence of acute HCV in MSM in some parts of the world which is largely linked to HIV coinfection, the presence of other STIs including syphilis and LGV, traumatic anal sex and use of recreational drugs.

Vertical (mother to infant) spread also occurs at a low rate (about 5% or less), but higher rates (up to 40%) are seen if the woman is both HIV- and HCV-positive. In all groups, transmission risk correlates with the presence of detectable HCVRNA in the mother's blood

The prevalence of positive HCV antibody in first-time donors in 2010 was 0.136%. The prevalence of HCV in Singapore is estimated to be around 0.1% of the general population, and 2% among persons with HIV infection, mostly among IDUs. There were 6 cases of acute hepatitis C reported in 2010.

CLINICAL FEATURES
Incubation period: 4 to 20 weeks

Symptoms
- >80% have asymptomatic acute infection
- Uncommon cases of acute icteric hepatitis

Signs
- Acute icteric hepatitis, see hepatitis A
- Chronic hepatitis, see hepatitis B

Complications
- Acute fulminant hepatitis is rare (<1% of all hepatitis C infections), but is more common after hepatitis A superinfection of chronic hepatitis C carriers
- Approximately 50-85% of infected patients become chronic carriers, a state which is normally asymptomatic but may cause nonspecific ill health. Type 1 genotype is more likely to clear spontaneously but leads to more severe chronic infection. Once established, the chronic carrier state rarely resolves spontaneously (0.02%/year). Symptoms and/or signs are worse if there is a high alcohol intake or other liver disease. Significant liver disease can be present in the 35% of carriers who have normal serum ALT levels
- Mortality in acute hepatitis is very low (<1%) but up to 30% of chronic carriers will progress to severe liver disease after 14-30 years of infection, with an increased risk of liver cancer (approximately 14% of all patients and up to 33% of those with cirrhosis). HIV coinfection also worsens the prognosis although this may be ameliorated to some degree by ART.
- Pregnancy Complications of acute icteric hepatitis: as for hepatitis A.

DIAGNOSIS

- Screening ELISA, confirmatory test e.g. recombinant immuno-blot assay (RIBA), third generation immunoassay or HCV-PCR for RNA. In HIV-infected patients with a low CD4 count (<200 cells/mm 3) the EIA may be negative and an HCV-PCR may be needed for diagnosis
- HCV-RNA will be positive after 2 weeks. HCV serology is usually positive (90%) 3 months after exposure but can take as long as 9 months
- Chronic infection is confirmed if HCV-RNA assay is positive 6 months after the first positive test. All patients being considered for therapy should have a viral RNA test to confirm viraemia and genotype assay

Other tests

- Acute infection: as for hepatitis A
- Chronic infection: as for hepatitis B

TREATMENT

General Measures

- Patients should not donate blood, semen or organs
- Patients should be given a detailed explanation of their condition, reinforced by giving them clear and accurate written information
- Acute hepatitis C infection is a notifiable disease
- Refer all HCV-positive patients to a liver specialist for consideration of treatment
- Patients with hepatitis C should be vaccinated against hepatitis A and B, given the high rate of fulminant hepatitis in co-infection hepatitis A & C and the worse prognosis of hepatitis B & C co-infection.

Acute Hepatitis

Acute hepatitis C infection is defined as the first six months of HCV infection following HCV exposure. However, most acute HCV infection goes undetected because the majority are asymptomatic.

With the advent and efficacy of direct acting antiviral (DAA) regimens for chronic HCV infection, there is less urgency to treat acute HCV infection. The Infectious Disease Society of America (IDSA) recommends waiting six months to evaluate for spontaneous clearance of HCV before considering initiating DAA.

In the following situations, treatment during acute phase may be preferable:

- Patients as risk of complications of HCV such as those with severe disease or have other comorbid liver disease
- Patients who pose a high risk of transmission to others

Chronic Infection

The advent of highly effective oral DAA has revolutionized the treatment of HCV infection, which was previously dependant on interferon. DAAs are drugs that target specific proteins of HCV (disrupting viral replication) and are the treatment of choice now. The goal of antiviral therapy is to eradicate HCV RNA, defined as undetectable HCV RNA 12 weeks after completing treatment.

The choice of DAA regimen depends on the genotype and patient factors such as liver function status and comorbidities, and is beyond the scope of this guidelines. Patients should be managed by a gastroenterologist with experience in managing hepatitis C infection.

CONSIDERATIONS IN PREGNANCY, BREAST FEEDING

- Routine testing for HCV infection is not recommended for all pregnant women. Pregnant women with a known risk factor for HCV infection should be offered counselling and testing
- There is at present no known way of reducing the risk of vertical transmission. Women should be informed of the potential risk of transmission in pregnancy **[II, B]**
- Breast feeding: there is no firm evidence of additional risk of transmission except, perhaps in women who are symptomatic with a high viral load **[III, B]**

MANAGEMENT OF SEXUAL CONTACTS

- Partner notification should be performed. Contact tracing to include any sexual contact (penetrative vaginal or anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious. The infectious period is from 2 weeks before the onset of jaundice in acute infection, or trace back to the likely time of infection (e.g. blood transfusion, first needle sharing) although this may be impractical for periods longer than two or three years. Consider testing children born to infectious women. **[IV, C]**
- There is currently no available vaccine or immunoglobulin preparation that will prevent transmission
- Sexual transmission should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided

SCREENING AND PRIMARY PREVENTION

Consider testing for hepatitis C in all IDUs, especially if equipment has been shared, in people sustaining a needle-stick injury if the donor HCV status is positive or unknown, sexual partners of HCV positive individuals, MSM, all HIV-positive patients, female sex workers, tattoo recipients, alcoholics and ex-prisoners.

Since 1993, all donated blood in Singapore has been screened for HCV.

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