PHC Chapter 12: Sexually transmitted infections

The syndromic approach to Sexually Transmitted Infections (STIs) diagnosis and management is to treat the signs or symptoms (syndrome) of a group of diseases rather than treating a specific disease. This allows for the treatment of one or more conditions that often occur at the same time and has been accepted as the management of choice.

Causative organisms and medicine management for STI syndromes:

ORGANISM	SYNDROME/S	MEDICINE MANAGEMENT
Neisseria gonorrhoeae	VDS, MUS, LAP	ceftriaxone + azithromycin *LoE:III*[1]
Chlamydia trachomatis	VDS, MUS, LAP, GUS, Bubo	azithromycin
Trichomonas vaginalis	VDS, LAP	metronidazole
Bacterial vaginosis (overgrowth of *Gardnerella vaginalis*, lactobacillus, anaerobes etc.)	VDS	metronidazole
Candida albicans	VDS	clotrimazole
Treponema pallidum	GUS	doxycycline/ benzathine benzylpenicillin
Herpes simplex	GUS	aciclovir
Haemophilus ducreyi	GUS, Bubo	azithromycin

It is important to take a good sexual history and undertake a thorough ano-genital examination in order to perform a proper clinical assessment. The history should include questions concerning symptoms, recent sexual history, sexual orientation, type of sexual activity (oral, vaginal, anal sex), the possibility of pregnancy (females), use of contraceptives including condoms, recent antibiotic history, antibiotic allergy, recent overseas travel and domestic violence. Refer to a social worker, as required.

Note: Standard referral letter for treatment failure must include the following:

» reason for referral: presumptive diagnosis (e.g. persistent cervicitis with suspected resistant gonorrhoea)
» clinical findings including speculum examination for vaginal discharge
» treatment history (including all medicines with dose and duration)
» details of notification and treatment history of partner(s)

Suspected STI in children should be referred to hospital for further investigation and management.

GENERAL MEASURES

» **C**ounselling and education, including HIV testing.
» **C**ondom promotion, provision and demonstration to reduce the risk of STIs.
» **C**ompliance/ adherence with treatment.
» **C**ontact treatment/ partner management.
» **C**ircumcision promotion (counselling to continue condom use).
» **C**ervical cancer screening.

Promote HIV counselling and testing.
For negative test results repeat test after 6 weeks, because of the window period.

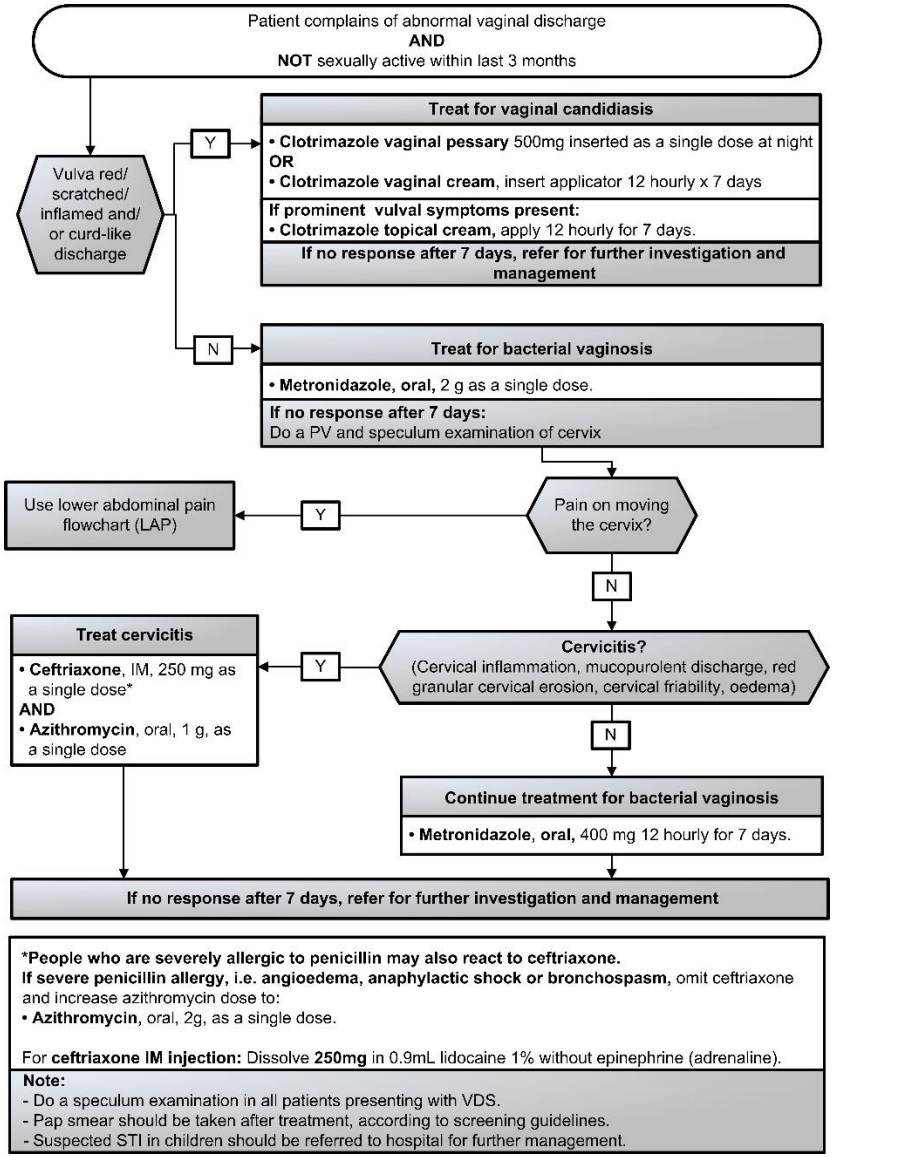
Benzathine benzylpenicillin

Benzathine benzylpenicillin remains the recommended treatment for syphilis. Azithromycin is not recommended for the treatment of syphilis in pregnancy as azithromycin does not effectively treat syphilis in the fetus, and resistance develops rapidly to macrolides. Therefore, benzathine benzylpenicillin should be reserved for use in pregnant women and children during times of a confirmed stock shortage.

12.1 VAGINAL DISCHARGE SYNDROME (VDS)

B37.3/N76.0/N89.8

12.1.1 SEXUALLY NON-ACTIVE WOMEN



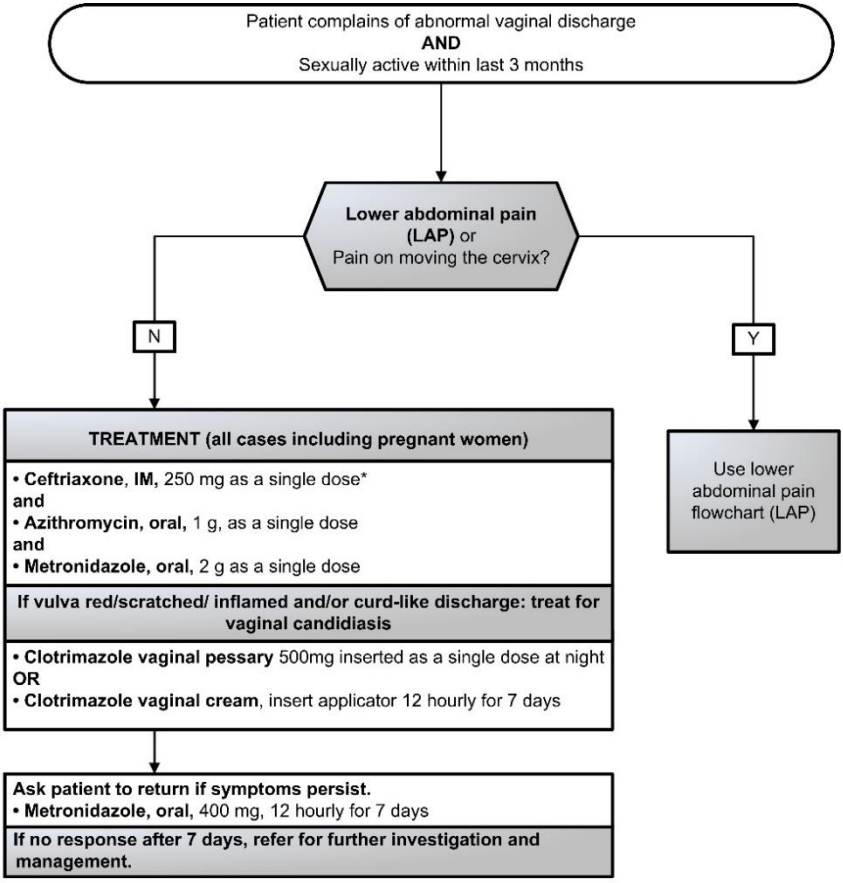
*People who are severely allergic to penicillin may also react to ceftriaxone.
If severe penicillin allergy, i.e. angioedema, anaphylactic shock or bronchospasm, omit ceftriaxone and increase azithromycin dose to:
• Azithromycin, oral, 2g, as a single dose.

For ceftriaxone IM injection: Dissolve 250mg in 0.9mL lidocaine 1% without epinephrine (adrenaline).

Note:
- Do a speculum examination in all patients presenting with VDS.
- Pap smear should be taken after treatment, according to screening guidelines.
- Suspected STI in children should be referred to hospital for further management.

LoE:III[2]

12.1.2 SEXUALLY ACTIVE WOMEN



***People who are severely allergic to penicillin may also react to ceftriaxone.**
If severe penicillin allergy, i.e. angioedema, anaphylactic shock or bronchospasm, omit ceftriaxone and increase azithromycin dose to:
• **Azithromycin,** oral, 2 g, as a single dose.

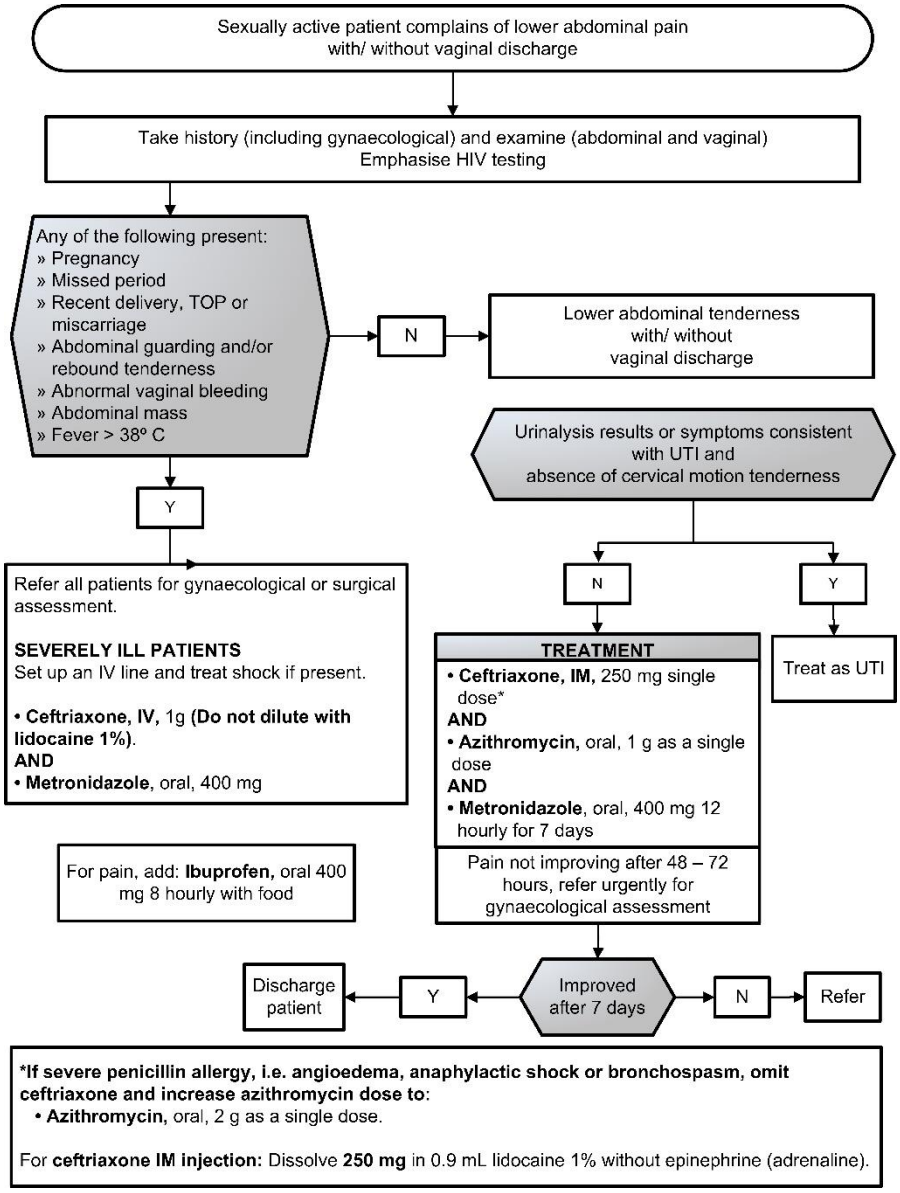
For **ceftriaxone IM injection:** Dissolve **250 mg** in 0.9 mL lidocaine 1% without epinephrine (adrenaline).

Note:
- Do a speculum examination in all patients presenting with VDS.
- Pap smear should be taken after treatment, according to screening guidelines.
- Suspected STI in children should be referred to hospital for further management.

LoE:III[3]

12.2 LOWER ABDOMINAL PAIN (LAP)

N73.9

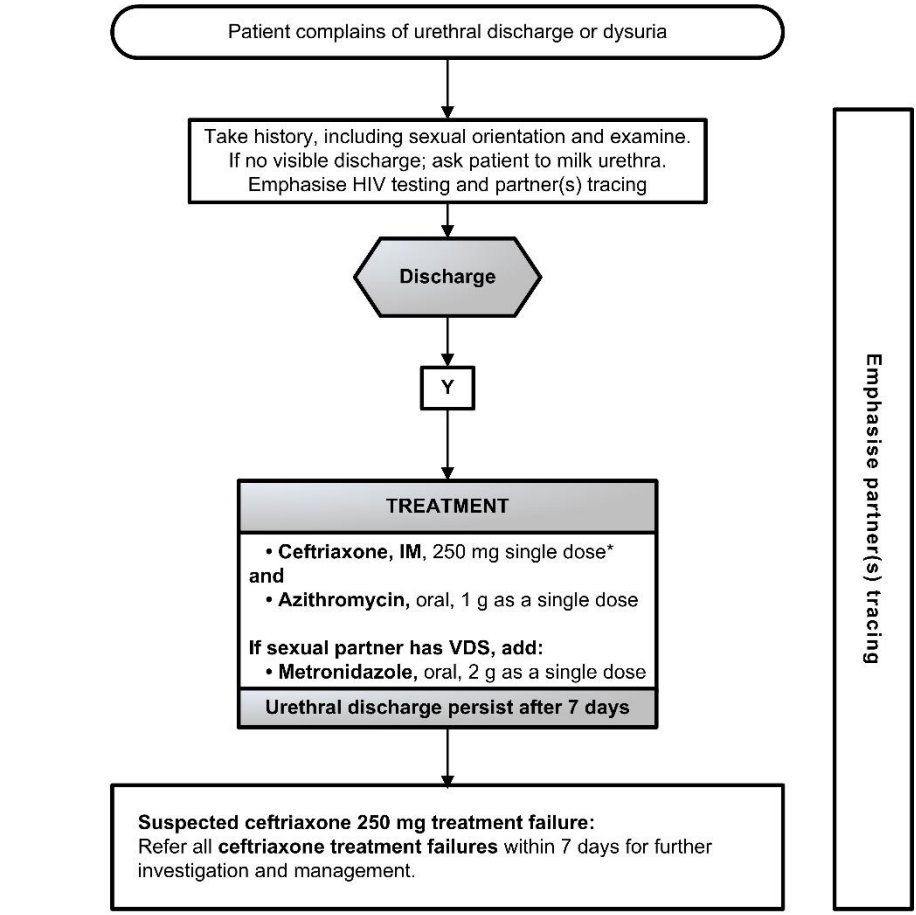


*If severe penicillin allergy, i.e. angioedema, anaphylactic shock or bronchospasm, omit ceftriaxone and increase azithromycin dose to:
- **Azithromycin,** oral, 2 g as a single dose.

For **ceftriaxone IM injection:** Dissolve **250 mg** in 0.9 mL lidocaine 1% without epinephrine (adrenaline).

12.3 MALE URETHRITIS SYNDROME (MUS)

A64 + N34.1



*If severe penicillin allergy, i.e. angioedema, anaphylactic shock or bronchospasm, omit ceftriaxone and increase azithromycin dose to:

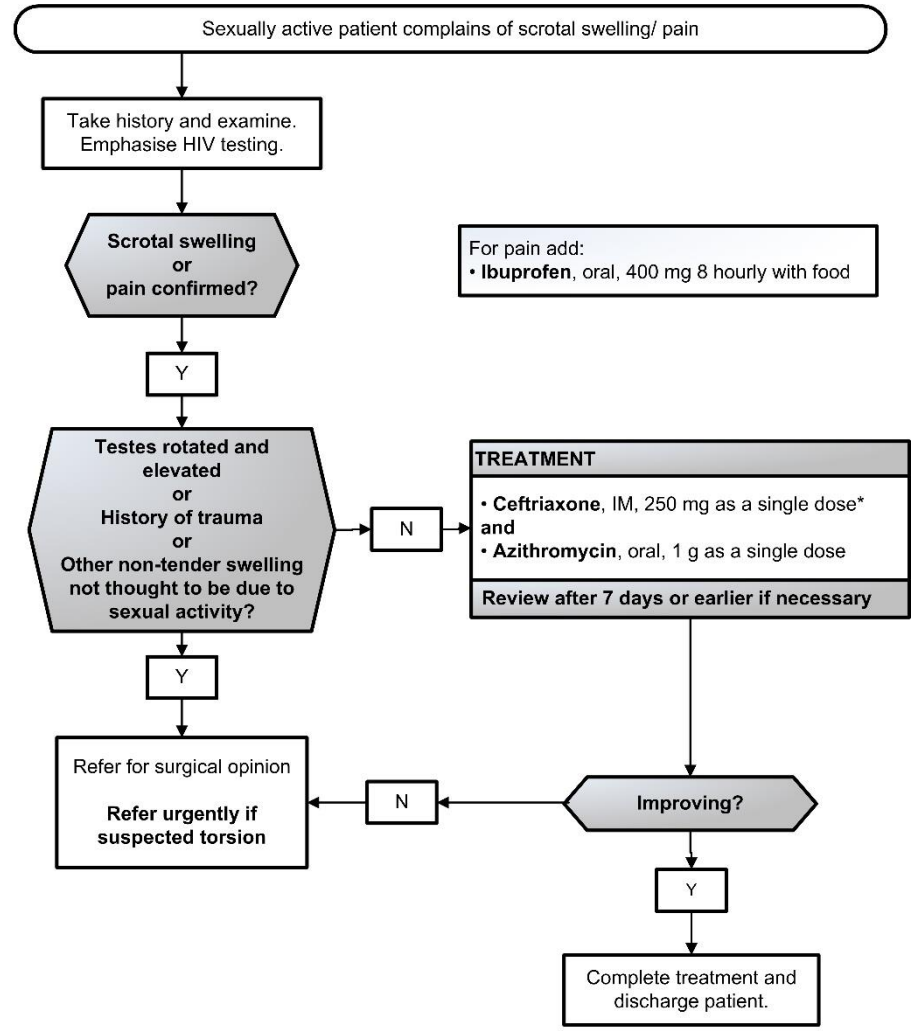
- **Azithromycin,** oral, 2 g as a single dose.

For **ceftriaxone IM injection:**

- Dissolve ceftriaxone **250 mg** in 0.9 mL lidocaine 1% without epinephrine (adrenaline).

12.4 SCROTAL SWELLING (SSW)

N45.1



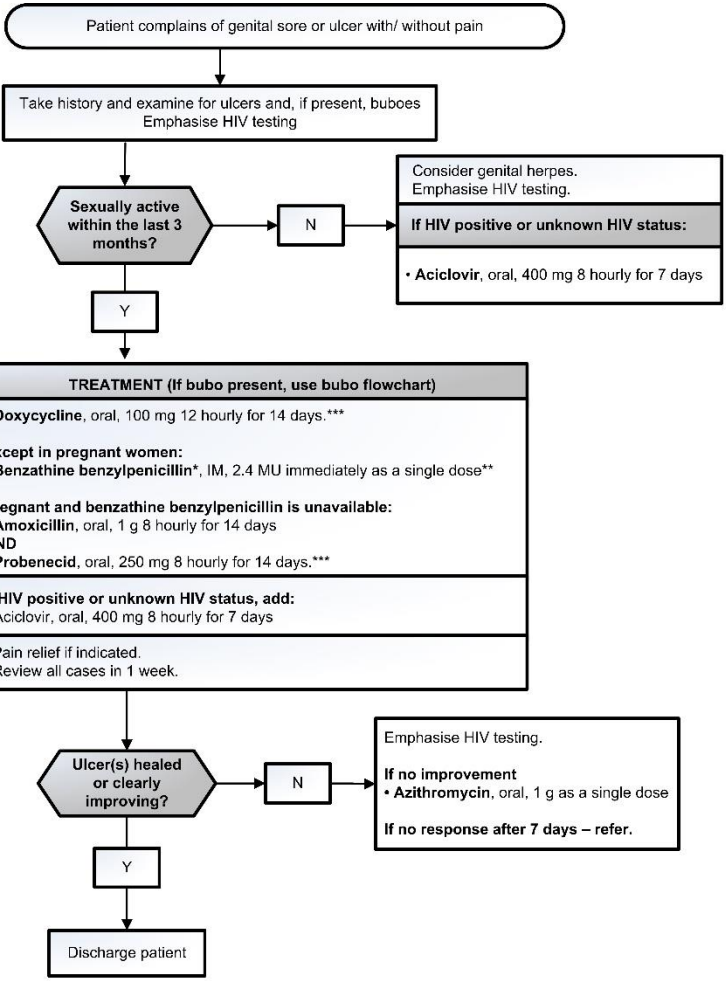
***If severe penicillin allergy, i.e. angioedema, anaphylactic shock or bronchospasm, omit ceftriaxone and increase azithromycin dose to:**
• **Azithromycin,** oral, 2 g as a single dose.

For **ceftriaxone IM injection:** dissolve **250 mg** in 0.9 mL lidocaine 1% without epinephrine (adrenaline).

12.5 GENITAL ULCER SYNDROME (GUS)

A60.9/A51.0

LoE:III[4]



***Penicillin allergic pregnant women: refer for confirmation of new syphilis infection and possible penicillin desensitisation.**

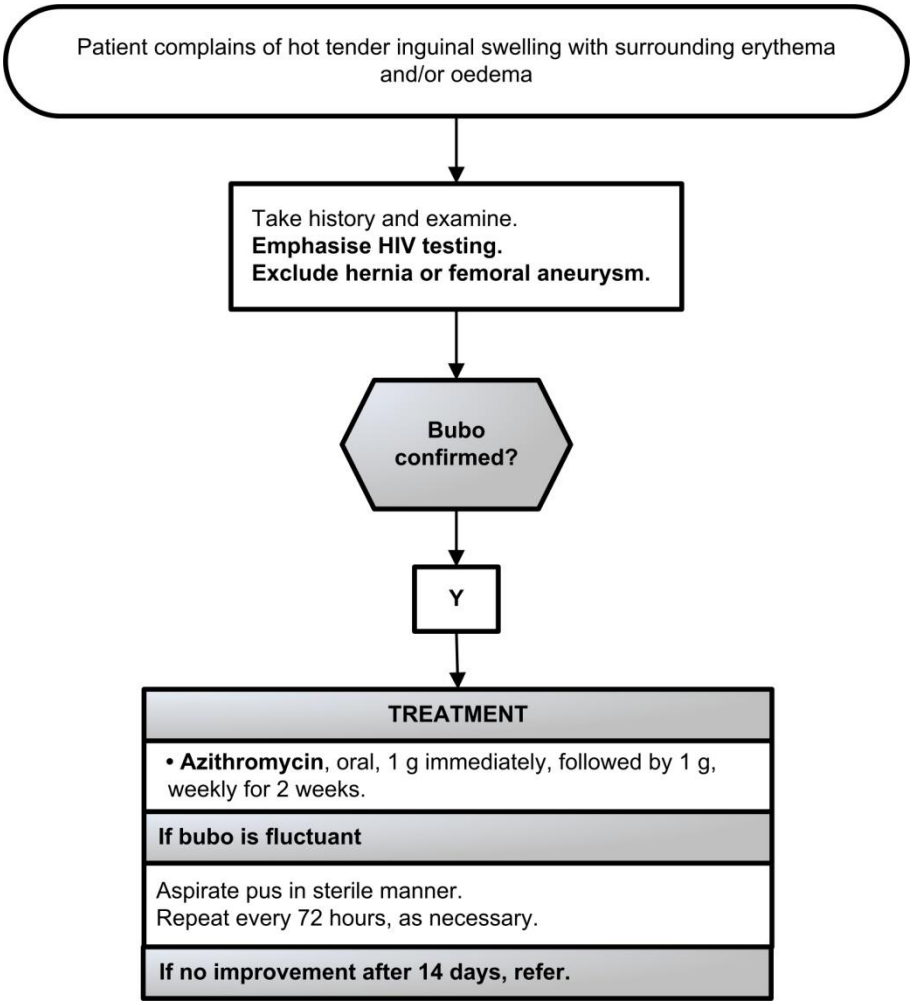
****For benzathine benzylpenicillin**, IM, 2.4 MU: Dissolve benzathine benzylpenicillin **2.4 MU** in 6 mL lidocaine 1% without epinephrine (adrenaline).

Note: Pregnant women presenting with genital ulcer(s) in the third trimester should be referred (risk of neonatal herpes).

LoE:II[5]

12.6 BUBO

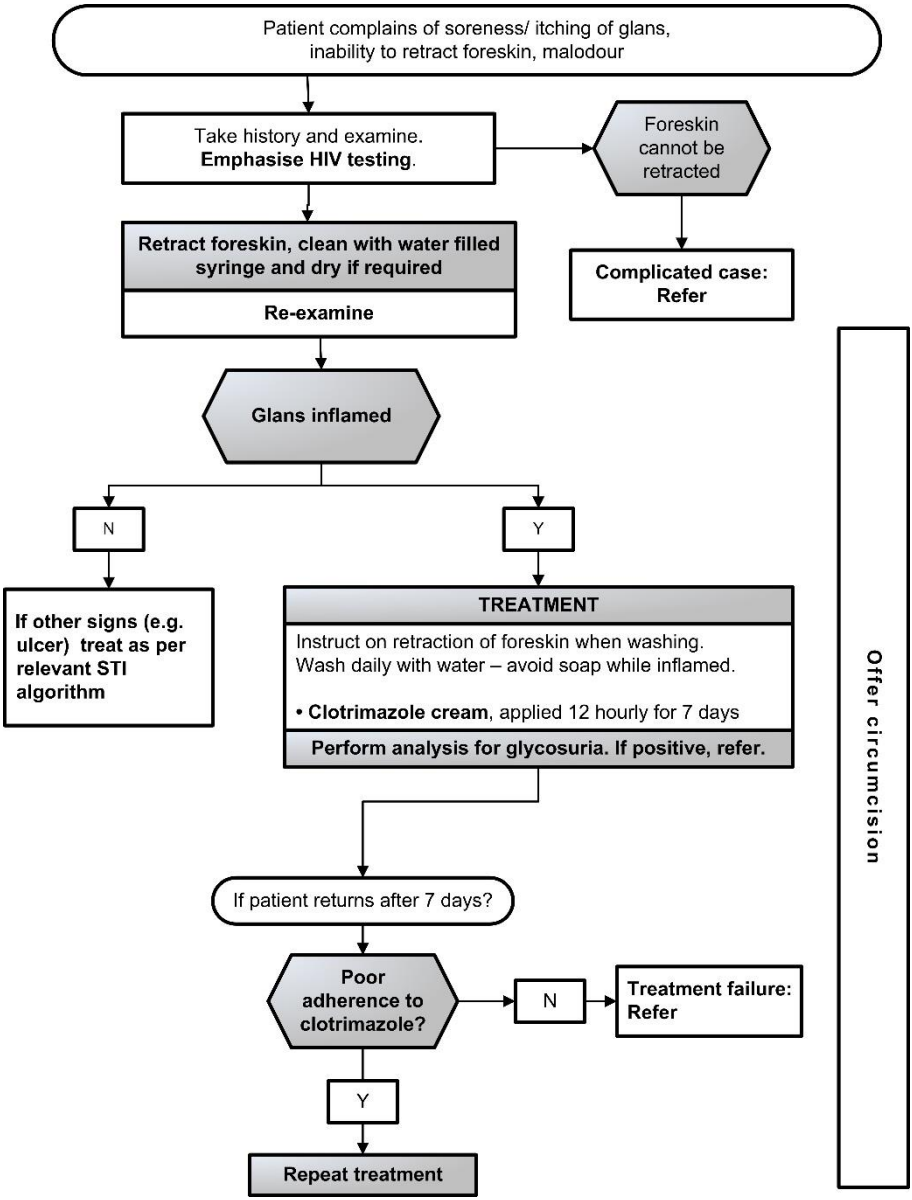
A58



LoE:III[6]

12.7 BALANITIS/BALANOPOSTHITIS (BAL)

N48.1



12.8 SYPHILIS SEROLOGY AND TREATMENT

A53.9

Syphilis serology

The Rapid Plasmin Reagin (RPR) measures disease activity, but is not specific for syphilis. False RPR-positive reactions may occur, notably in patients with connective tissue disorders (false positive reactions are usually low titre <1:8). For this reason, positive RPR results should be confirmed due to syphilis by further testing of the serum with a specific treponemal test, e.g.:

» *Treponema pallidum* haemagglutination (TPHA) assay.
» *Treponema pallidum* particle agglutination (TPPA) assay.
» Fluorescent Treponemal Antibody (FTA) assay.
» *Treponema pallidum* ELISA.
» Rapid treponemal antibody test (TPAb)

Screening can also be done the other way around starting with a specific treponemal test followed by a RPR in patients who have a positive specific treponemal test. This is sometimes referred to as the "reverse algorithm".

- Once positive, specific treponemal tests generally remain positive for life and therefore the presence of specific treponemal antibodies cannot differentiate between current and past infections
- A person with previously successfully treated syphilis will retain lifelong positive specific treponemal test results.

The RPR can be used:

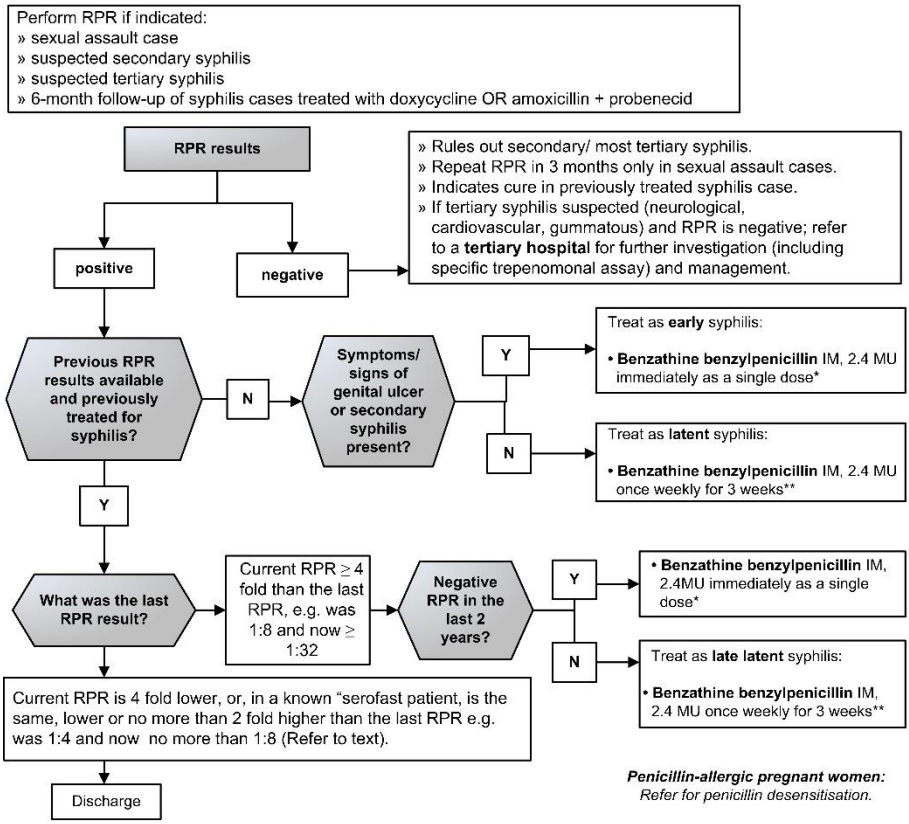
» To determine if the patient's syphilis disease is active or not,
» To measure a successful response to therapy (at least a fourfold reduction in titre, e.g. 1:256 improving to 1:64), or
» To determine a new re-infection.

Some patients, even with successful treatment for syphilis, may retain life-long positive RPR results at low titres (≤1:8), which do not change by more than one dilution difference (up or down) over time (so-called serofast patients).

Note:

» Up to 30% of early primary syphilis cases, i.e. those with genital ulcers may have a negative RPR.
» The RPR is always positive in the secondary syphilis stage and remains high during the first two (infectious) years of syphilis. *LoE:II*[7]

For syphilis treatment in pregnancy, see Section 6.4.4: Syphilis in pregnancy.



***Early syphilis treatment:**

Severe penicillin allergy or benzathine benzylpenicillin is unavailable:

- **Doxycycline,** oral, 100 mg 12 hourly for 14 days.

Pregnant or benzathine benzylpenicillin is unavailable:

- **Amoxicillin**, oral, 1 g 8 hourly for 14 days

AND

- **Probenecid**, oral 250 mg 8 hourly for 14 days.

****Latent/ late latent syphilis treatment:**

Severe penicillin allergy or benzathine benzylpenicillin is unavailable:

- **Doxycycline**, oral, 100 mg 12 hourly for 30 days.

Pregnant or benzathine benzylpenicillin is unavailable:

- **Amoxicillin**, oral, 1 g 8 hourly for 28 days

AND

- **Probenecid,** oral 250 mg 8 hourly for 28 days.

For **benzathine benzylpenicillin**, IM, 2.4 MU: Dissolve **2.4 MU** in 6 mL lidocaine 1% without epinephrine (adrenaline).

MEDICINE TREATMENT

Early syphilis treatment
Check if treated at initial visit.

- Benzathine benzylpenicillin, IM, 2.4 MU immediately as a single dose A .
  - Dissolve benzathine benzylpenicillin, IM, 2.4 MU in 6 mL lidocaine 1% without adrenaline (epinephrine).

In penicillin-allergic patients or if benzathine benzylpenicillin is unavailable:
Z88.0

- Doxycycline, oral, 100 mg 12 hourly for 14 days A . *LoE:III*[8]

If pregnant and benzathine benzylpenicillin is unavailable:

- Amoxicillin, oral 1 g 8 hourly for 14 days (Doctor initiated) A .

AND

- Probenecid, oral 250 mg, 8 hourly for 14 days (Doctor initiated). *LoE:III*[9]

If penicillin-allergic and pregnant: Refer for penicillin desensitisation.

Late/ late latent syphilis treatment
Check if treatment was commenced at initial visit.

- Benzathine benzylpenicillin, IM, 2.4 MU once weekly for 3 weeks A .
  - Dissolve benzathine benzylpenicillin, IM, 2.4 MU in 6 mL lidocaine 1% without adrenaline (epinephrine).

In penicillin-allergic patients or if benzathine benzylpenicillin is unavailable:
Z88.0

- Doxycycline, oral, 100 mg 12 hourly for 30 days A . *LoE:III*[10]

If pregnant and benzathine benzylpenicillin is unavailable:

- Amoxicillin, oral 1 g 8 hourly for 28 days (Doctor initiated) A .

AND

- Probenecid, oral 250 mg, 8 hourly for 28 days (Doctor initiated). *LoE:III*[11]

If penicillin-allergic and pregnant: Refer for penicillin desensitisation.

REFERRAL

» Tertiary syphilis: neurosyphilis, cardiovascular syphilis; gummatous syphilis.
» Clinical congenital syphilis.

12.9 TREATMENT OF MORE THAN ONE STI SYNDROME

STI SYNDROMES	TREATMENT (NEW EPISODE)
MUS + SSW	Treat according to SSW flow chart.
MUS + BAL	Treat according to MUS flow chart. **AND** • Clotrimazole cream, 12 hourly for 7 days.
MUS + GUS	• Ceftriaxone, IM, 250 mg immediately as a single dose W . **AND** • Azithromycin, oral, 1 g as a single dose W . **AND**

	• Aciclovir, oral, 400 mg 8 hourly for 7 days*.
VDS + LAP	Treat according to LAP flow chart. **AND** Treat for candidiasis, if required (see VDS flow chart).
VDS + GUS	• Ceftriaxone, IM, 250 mg immediately as a single dose W. **AND** • Metronidazole, oral, 2 g immediately as a single dose A. **AND** • Azithromycin, oral, 1 g as a single dose W. **AND** • Aciclovir, oral, 400 mg 8 hourly for 7 days*. **AND** Treat for candidiasis, if required (see VDS flow chart).
LAP+ GUS	• Ceftriaxone, IM, 250 mg immediately as a single dose W. **AND** • Metronidazole, oral, 400 mg 12 hourly for 7days A. **AND** • Aciclovir, oral, 400 mg 8 hourly for 7 days*. **AND** • Azithromycin, oral, 1 g as a single dose W.
SSW+ GUS	• Ceftriaxone, IM, 250 mg immediately as a single dose W. **AND** • Aciclovir, oral, 400 mg 8 hourly for 7 days*. **AND** • Azithromycin, oral, 1 g as a single dose W.
***Treat with aciclovir only if HIV status is positive or unknown.** ****Penicillin allergic men and non-pregnant women avoid ceftriaxone and refer to relevant algorithms.** **Penicillin allergic pregnant/breastfeeding women, refer for penicillin desensitisation.**	

12.10 TREATMENT OF PARTNERS

Syndrome	Asymptomatic partner	Symptomatic partner
VDS	• Ceftriaxone, IM, 250 mg immediately as a single dose. **AND** • Metronidazole, oral, 2 g immediately as a single dose. **AND** • Azithromycin, oral, 1 g as a single dose.	• Ceftriaxone, IM, 250 mg immediately as a single dose. **AND** • Metronidazole, oral, 2 g immediately as a single dose. **AND** • Azithromycin, oral, 1 g as a single dose. PLUS treatment for syndrome present if not included in the above.
LAP	• Ceftriaxone, IM, 250 mg immediately as a single dose. **AND**	• Ceftriaxone, IM, 250 mg immediately as a single dose. **AND**

	• Metronidazole, oral, 2 g immediately as a single dose. **AND** • Azithromycin, oral, 1 g as a single dose.	• Metronidazole, oral, 2 g immediately as a single dose. **AND** • Azithromycin, oral, 1 g as a single dose. PLUS treatment for syndrome present if not included in the above.
MUS	• Ceftriaxone, IM, 250 mg immediately as a single dose. **AND** • Azithromycin, oral, 1 g as a single dose.	• Ceftriaxone, IM, 250 mg immediately as a single dose. **AND** • Azithromycin, oral, 1 g as a single dose. PLUS treatment for syndrome present if not included in the above (see VDS flow chart).
Scrotal swelling	• Ceftriaxone, IM, 250 mg immediately as a single dose. **AND** • Azithromycin, oral, 1 g as a single dose.	• Ceftriaxone, IM, 250 mg immediately as a single dose. **AND** • Azithromycin, oral, 1 g as a single dose. PLUS treatment for syndrome present if not included in the above.
GUS	• Doxycycline, oral, 100 mg 12 hourly for 14 days. <u>Except pregnant women:</u> • Benzathine benzylpenicillin, IM, 2.4 MU immediately as a single dose. o Dissolve benzathine benzylpenicillin, IM, 2.4 MU in 6 mL lidocaine 1% without epinephrine (adrenaline). (If pregnant and benzathine benzylpenicillin is unavailable, see syphilis flow chart).	• Doxycycline, oral, 100 mg 12 hourly for 14 days. <u>Except pregnant women:</u> • Benzathine benzylpenicillin, IM, 2.4 MU immediately as a single dose. o Dissolve benzathine benzylpenicillin, IM, 2.4 MU in 6 mL lidocaine 1% without epinephrine (adrenaline). PLUS treatment for syndrome present if not included in the above. (If pregnant and benzathine benzylpenicillin is unavailable, see syphilis flow chart).
Bubo	• Azithromycin, oral, 1 g as a single dose.	• Azithromycin, oral, 1 g as a single dose. PLUS treatment for syndrome present if not included in the above.

LoE:III[12]

12.11 GENITAL MOLLUSCUM CONTAGIOSUM (MC)

B08.1

DESCRIPTION

This is a viral infection which can be transmitted sexually and non-sexually. It is usually self-limiting but can be progressive in an advanced stage of immunodeficiency.
Clinical signs include papules at the genitals or other parts of the body.
The papules usually have a central dent (umbilicated papules).

MEDICINE TREATMENT

- Tincture of iodine BP, topical.
  - Apply with an applicator to the core of the lesions.

12.12 GENITAL WARTS (GW): CONDYLOMATA ACCUMINATA

A63.0

DESCRIPTION

The clinical signs include:

» Warts on the ano-genital areas, vagina, cervix, meatus or urethra.
» Warts can be soft or hard.

In most cases, warts resolve without treatment after 2 years in non-immunosuppressed patients.

GENERAL MEASURES

» If warts do not look typical or are fleshy or wet, perform a RPR test to exclude secondary syphilis, which may present with similar lesions.
» Emphasise HIV testing.

REFERRAL

» All patients with:
  - warts > 10 mm
  - inaccessible warts, e.g. intra-vaginal or cervical warts
  - numerous warts
  -

12.13 PUBIC LICE (PL)

B85.3

DESCRIPTION

Infestation of lice mostly confined to pubic and peri-anal areas, and occasionally involves eyelashes.

The bites cause intense itching, which often results in scratching with bacterial super-infection.

GENERAL MEASURES

Thoroughly wash clothing and bed linen that may have been contaminated by the patient in the 2 days prior to the start of treatment in hot water and then iron.

MEDICINE TREATMENT

- Benzyl benzoate 25%
  - Apply to affected area.
  - Leave on for 24 hours, then wash thoroughly.
  - Repeat in 7 days.

Pediculosis of the eyelashes or eyebrows

- Yellow petroleum jelly (Note: Do not use white petroleum jelly near the eyes).
  - Apply to the eyelid margins (cover the eyelashes) daily for 10 days to smother lice and nits.
  - Do not apply to eyes.

LoE:III

REFERRAL

All children with lice on pubic, perianal area and eyelashes to exclude sexual abuse.

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Syphilis serology (RPR follow-up test in doxycycline-treated patients not recommended): Salado-Rasmussen K, Hoffmann S, Cowan S, Jensen JS, Benfield T, Gerstoft J, Katzenstein TL. Serological Response to Treatment of Syphilis with Doxycycline Compared with Penicillin in HIV-infected Individuals. Acta Derm Venereol. 2016 Aug 23;96(6):807-11. https://www.ncbi.nlm.nih.gov/pubmed/26568359

Syphilis serology (RPR follow-up test in doxycycline-treated patients not recommended): Dai T, Qu R, Liu J, Zhou P, Wang Q. Efficacy of Doxycycline in the Treatment of Syphilis. Antimicrob Agents Chemother. 2016 Dec 27;61(1). pii: e01092-16. https://www.ncbi.nlm.nih.gov/pubmed/27795370

[8] Doxycycline, oral (Early syphilis treatment - penicillin allergic/benzathine benzylpenicillin unavailable): World Health Organization. WHO guidelines for the treatment of Treponemapallidum (syphilis), 2016. http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf

[9] Amoxicillin, oral + probenecid, oral (Early syphilis treatment - pregnant/benzathine benzylpenicillin unavailable): Tanizaki R, Nishijima T, Aoki T, Teruya K, Kikuchi Y, Oka S, et al. High-dose oral amoxicillin plus probenecid is highly effective for syphilis in patients with HIV infection. Clin Infect Dis. 2015;61(2):177-83. https://www.ncbi.nlm.nih.gov/pubmed/25829004

Amoxicillin, oral + probenecid, oral (Early syphilis treatment - pregnant/benzathine benzylpenicillin unavailable): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Amoxicllin+probenecid for syphilis in pregnant women, January 2018. http://www.health.gov.za/

[10] Doxycycline, oral: Late latent syphilis treatment - penicillin allergic: World Health Organization. WHO guidelines for the treatment of Treponema pallidum (syphilis), 2016. http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf

[11] Amoxicillin, oral + probenecid, oral (Late latent syphilis treatment - pregnant/benzathine benzylpenicillin unavailable): Tanizaki R, Nishijima T, Aoki T, Teruya K, Kikuchi Y, Oka S, et al. High-dose oral amoxicillin plus probenecid is highly effective for syphilis in patients with HIV infection. Clin Infect Dis. 2015;61(2):177-83. https://www.ncbi.nlm.nih.gov/pubmed/25829004

Amoxicillin, oral + probenecid, oral (Late latent syphilis treatment - pregnant/benzathine benzylpenicillin unavailable): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Amoxicllin+probenecid for syphilis in pregnant women, January 2018. http://www.health.gov.za/

[12] STI partner treatment: Centers for Disease Control and Prevention. 2015 Sexually Transmitted Diseases Treatment Guidelines. https://www.cdc.gov/std/tg2015/

REPUBLIC OF SOUTH AFRICA PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 12: SEXUALLY TRANSMITTED INFECTIONS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2016 -2018)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the dental and oral conditions chapter.

SECTION	MEDICINE/MANAEGEMENT	ADDED/DELETED/NOT ADDED/ AMENDED/ RETAINED
General		
– *Treatment of N. gonorrhoeae*	Cefixime, oral	Not added
	Ceftriaxone, IM	Retained
	Azithromycin, oral	Retained
12.1 Vaginal discharge syndrome (VDS)		
	Age cut-off criterion	Deleted from VDS algorithm
	Sexual activity criterion	Added to VDS algorithm
	Clotrimazole + metronidazole dual therapy	Amended to monotherapy directed syndromic management
	Speculum examination	Added to VDS algorithm to differentiate between cervicitis and vaginitis
	Clotrimazole, topical	Added
	Fluconazole, oral	Not added
12.2 Lower abdominal pain (LAP)		
– *Severely ill patients: Severe penicillin allergy*	Gentamicin, IV	Not added
	Clindamycin, IV	Not added
	Ciprofloxacin, oral	Not added
	Ceftriaxone, IV, 1 g	Retained
	Metronidazole, oral, 400mg	Retained
12.5 Genital ulcer syndrome (GUS)		
	Ceftriaxone, IM	Not added
	Benzathine benzylpenicillin, IM 2.4MU	Retained and amended
	Doxycycline, oral	Amended
– *Aciclovir-resistant ulcers*	Azithromycin, oral, 1 g	Retained and directions for use amended
12.6 Bubo		
	Azithromycin, oral, 1g	Dosing amended
12.7 Balanitis/balanoposthitis (BAL)		
	Benzathine benzylpenicillin, IM, 2.4MU	Deleted
12.8 Syphilis serology and treatment		
– *Early syphilis and Late latent syphilis treatment: Severe penicillin allergy and if benzathine benzylpenicillin is unavailable*	Doxycycline, oral	Added
– *Pregnant women*	Amoxicillin, oral	Added
	Probenicid, oral	Added
– *Serology testing*	RPR testing	Amended (i.e. Follow up serology for all syphilis cases treated with oral antibiotics)
12.10 Treatment of partners		
	Ceftriaxone, 250 mg, IM	Added
	Azithromycin, 1 g, oral	Added
	Metronidazole, 2g, oral	Added
	Doxcycyline, oral	Added
	Benzathine benzylpenicillin, IM 2.4 mu	Added
	Lidocaine 1% without epinephrine (adrenaline)	Added
12.13 Pubic lice		
– *Pediculosis of the eyelashes/ eyebrows*	Yellow petroleum jelly	Added
	White petroleum jelly	Deleted

Acknowledgement: National Institute Communicable Diseases.

GENERAL

Delineation of management of STIs according to level of care

Algorithms were amended to provide guidance at primary level of care. Further investigation and management of treatment-resistant cases to be done at secondary level; to be included in the Adult Hospital level STGs and EML, as currently management is guided by levels of care and relevant guidance should be included in the appropriate guidelines.

Level of Evidence: III Expert opinion

Causative pathogens for STI syndromes

The following summary was included in the STG to assist the healthcare worker:

ORGANISM	SYDROME/S	MEDICINE MANAGEMENT
Neisseria gonorrhoeae	VDS, MUS, LAP	ceftriaxone + azithromycin
Chlamydia trachomatis	VDS, MUS, LAP	azithromycin
Trichomonas vaginalis	VDS, LAP	metronidazole
Bacterial vaginosis (overgrowth of Gardnerella vaginalis, lactobacillus, anaerobes etc)	VDS	metronidazole
Candida albicans	VDS	clotrimazole
Treponema pallidum	GUS	doxycyline/benzathine penicillin
Herpes simplex	GUS	aciclovir
Haemophilus ducreyi	GUS	azithromycin

Point of care testing

Rapid diagnostic testing of STIs not currently being implemented by the NDoH STI Programme. The tests need to be validated for use in the clinic setting prior to national implementation; and a proficiency testing scheme must be developed for quality assurance of results at participating clinics.

Treatment of *Neisseria gonorrhoeae*

Cefixime, oral: *not added*
Ceftriaxone, IM: *retained*
Azithromycin, oral: *retained*

External motivation was received from Merck (Pty) Ltd, for cefixime + azithromycin for eradication of *Neisseria gonorrhoeae* in the syndromic management of vaginal discharge syndrome (VDS), male urethritis syndrome (MUS) and lower abdominal pain (LAP).

Multi-drug and extensively-drug resistant gonorrhoea: Historically, cefixime was recommended to treat *N. gonorrhoeae* due to widespread resistance to fluoroquinolones. However, in 2001, Japan[1] [2] reported cefixime treatment failures (including extended cefixime regimens)[3], that were susceptible to ceftriaxone. Locally, NICD[4] [5] received reports of 4 cefixime treatment failure cases. These isolates were laboratory confirmed to be resistant to cefixime and susceptible to ceftriaxone. And, in 2014

[1] Ito M et al. Remarkable increase in central Japan in 2001-2002 of Neisseria gonorrhoeae isolates with decreased susceptibility to penicillin, tetracycline, oral cephalosporins, and fluoroquinolones. Antimicrob Agents Chemother. 2004 Aug;48(8):3185-7. https://www.ncbi.nlm.nih.gov/pubmed/15273147

[2] Tanaka M, et al. A remarkable reduction in the susceptibility of Neisseria gonorrhoeae isolates to cephems and the selection of antibiotic regimens for the single-dose treatment of gonococcal infection in Japan. J Infect Chemother. 2002 Mar;8(1):81-6. https://www.ncbi.nlm.nih.gov/pubmed/11957125

[3] Yokoi S,et al.. Threat to cefixime treatment for gonorrhea. Emerg Infect Dis. 2007 Aug;13(8):1275-7. https://www.ncbi.nlm.nih.gov/pubmed/17953118

[4] Lewis DA, et al. Phenotypic and genetic characterization of the first two cases of extended-spectrum-cephalosporin-resistant Neisseria gonorrhoeae infection in South Africa and association with cefixime treatment failure. J Antimicrob Chemother. 2013 Jun;68(6):1267-70. https://www.ncbi.nlm.nih.gov/pubmed/23416957

[5] Lewis DA. Gonorrhoea resistance among men who have sex with men: what's oral sex got to do with it? South Afr J Epidemiol Infect 2013;28(2):77. https://journals.co.za/content/mp_sajei/28/2/EJC138699

ceftriaxone, IM was recommended as dual therapy with azithromycin for syndromic management of STIs.[6]

Ceftriaxone PK/PD: It was reported that ceftriaxone's more favourable pharmacokinetic/ pharmacodynamics (PK/PD) profile compared with cefixime would probably result in greater bacteriological activity leading to better cure rate than cefixime and reduce the risk of the emergence of resistance.[7] Ceftriaxone also has greater affinity than cefixime for the mosaic penicillin-binding protein 2 that confers resistance to extended spectrum cephalosporins.[8] Ceftriaxone MICs are generally lower than cefixime for *N. gonorrhoeae*.[9]

Comparative prices (direct medicine prices): Replacing cefixime with ceftriaxone + lidocaine 1% would result in additional costs incurred.

Medicine	Price	Data source
Cefixime, oral, 400 mg tablet	**R 15.00**	Merck (Pty) Ltd quote, 20 December 2017.[10]
Ceftriaxone, IM, 250 mg diluted in 0.9 mL lidocaine 1%:	**R 12.35**	
Treatment regimen components:		
• *Ceftriaxone, 250 mg*	*R 3.67*	Contract circular RT301-2017
• *Lidocaine 1% without lidocaine, 0.9 mL (including 10% for wastage = 1 mL in total)*[11]	*R 0.44*	Contract circular HP06-2017SVP
• *Syringe and webcol*	*R 2.00*	
• *Clinical nurse practitioner time (2 minutes)*[12]	*R 6.24*	DPSA, OSD scale, April 2017

Note: Costs for antimicrobial resistance requiring additional susceptibility laboratory tests and up referral to secondary level of care for further management was not considered.

Recommendation: Ceftriaxone, IM be retained as the cephalosporin of choice as part of presumptive dual therapy for sexually transmitted infections.

Rationale: Antimicrobial resistant reports of *Neisseria gonorrhoeae* to cefixime globally and locally, greater affinity of ceftriaxone to causative organism warrants recommendation of ceftriaxone, IM. In addition, ceftriaxone, IM is cheaper than cefixime, oral.

Level of Evidence: III Case reports, Antimicrobial susceptibility study, Expert opinion

12.1 VAGINAL DISCHARGE SYNDROME (VDS)

Age cut-off criterion: *deleted from VDS algorithm*
Sexual activity criterion: *added to VDS algorithm*
Cotrimazole+metronidazole dual therapy: *amended to monotherapy directed syndromic management*
Speculum examination: *added to VDS algorithm to differentiate between cervicitis and vaginitis*

A: AGE CUT-OFF CRITERION

Previous age cut-off (<35 years) criterion: Unpublished surveillance data for VDS at Alexander Health Centre, Gauteng (2007 -2012) shared by NICD: Centre for STI and HIV informed the age cut-off criterion of < 35 years of age. In that survey, N gonorrhoea and C trachomatis were infrequent causes of VDS women > 35 years of age.

[6] PHC STGs and EML, 2014
[7] Chisholm SA, et al. Cephalosporin MIC creep among gonococci: time for a pharmacodynamic rethink? J AntimicrobChemother. 2010 Oct;65(10):2141-8. https://www.ncbi.nlm.nih.gov/pubmed/20693173
[8] Zhao S, Duncan M, Tomberg J, Davies C, Unemo M, Nicholas RA. Genetics of chromosomally mediated intermediate resistance to ceftriaxone and cefixime in Neisseria gonorrhoeae. Antimicrob Agents Chemother. 2009 Sep;53(9):3744-51. https://www.ncbi.nlm.nih.gov/pubmed/19528266
[9] Unemo M, Nicholas RA. Emergence of multidrug-resistant, extensively drug-resistant and untreatable gonorrhea. Future Microbiol. 2012 Dec;7(12):1401-22. https://www.ncbi.nlm.nih.gov/pubmed/23231489
[10] Data on file at NDoH, EDP.
[11] Contract circular HP062017SVP: Lidocaine 1% 20 mL = R 8.71.
[12] Department of Public Service and Administration. Occupation Specific Dispensations Scales, Aril 2017: Clinical Nurse Practitioner (Grade 1) – annual salary of R 394,665.00; assuming 42-hour week (2184 hours/annum) and that it takes an additional minute and a half to administer ceftriaxone IM, 250 mg vs directly observed treatment of cefixime, oral = R 4.52 for 1.5 minutes.

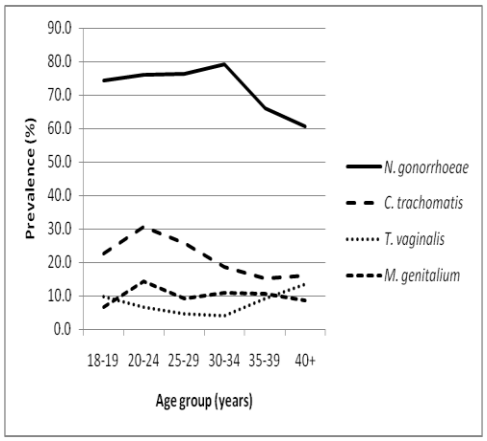


Figure 1a: Men

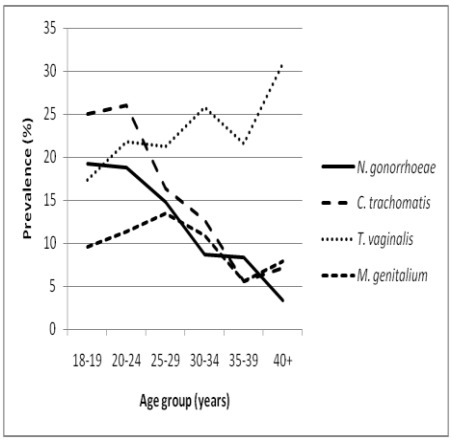


Figure 1b: Women

Figure 1a & 1 b: Prevalence of *Neisseria gonorrhoeae*, *Chlamydia trachomatis, Trichomoniais vaginalis and Mycoplasma genitalium*by age group for men (n=1,218) and women (n=1,232) with genital discharges - combined survey data from six annual surveys undertaken from January to April each year in Alexandra Health Centre, 2007-2012.

Surveillance data for period 2015-2016 (Alexandra Health Centre): Surveillance data of women presenting with VDS at Alexandra Health Centre(n=771) for the period January 2015 to September 2016 provided by NICD/NHLS, stratified in 4 groups showed the following % of women > 35 years of age:

1. Bacterial vaginosis or candidiasis and no STI co-infection: 20%
2. Bacterial vaginosis or candidiasis and STI co-infection: 14%
3. STI infection only: 19%
4. No pathogens detected: 29%

National Surveillance data: The PHC 2014 VDS algorithm does not included treatment for gonorrhoea/chlamydia for women older than 35. However, local surveillance data from the 2014-2015 National Aetiological Surveillance (NAS) study (n=801)[13] shows that the median age of women with non-STI causes (BV/ Candidiasis) of VDS was 29 years (IQR 24 to 36); n=271, whereas that of women harbouring one or more STI pathogens was 26 years (IQR 22 to 34), n=87; the difference was not statistically significant (p=0.095) (801 VDS cases tested).

Accuracy of using age to determine STI aetiology: Sub-analysis of the national aetiology sentinel (NAS) surveillance data (April 2014 – September 2015) suggests that the overall accuracy (area under the ROC curve) of using age to predict presence of GC/CT infections was only 66.2% (95% CI 61.6 to 70.7%). Details of this analysis, using data from the NAS survey and provided by NICD (embargoed, to be published) appear in the table and figure below:

Performance of different age cut offs for diagnosis of GC/CT infections

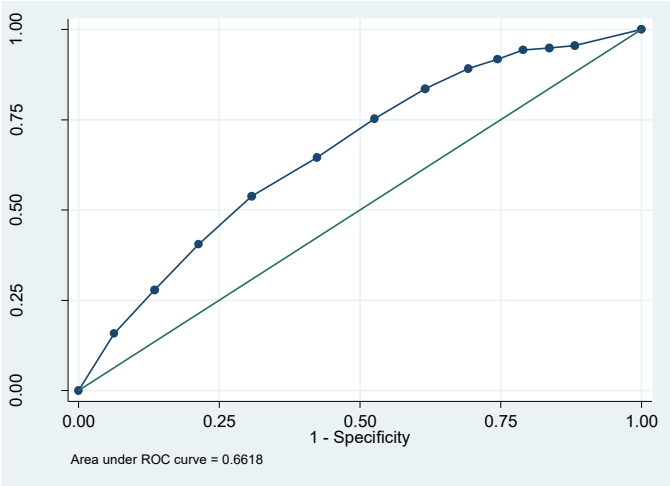
Age cut offs	Sensitivity of picking up GC/CT (%)	Specificity of picking up GC/CT (%)	Correctly classified (%)
>=50	100	0.0	20.9
47 - 49	95.6	11.9	29.3
44 - 46	94.9	16.4	32.8
41 - 43	94.3	21.0	36.3
38 - 40	91.8	25.5	39.4
35 - 37	89.2	30.7	42.9
32 - 34	83.5	38.4	47.8
29 - 31	75.3	47.4	53.2
26 - 28	64.6	57.6	59.1

[13] National Institute for Communicable Diseases. Report on the Sentinel Surveillance of Sexually Transmitted Infection Syndrome Aetiologies and HPV Genotypes among Patients attending Public Health Facilities in South Africa (April 2014 – September 2015), embargoed, to be published.

24 - 25	53.8	69.3	66.1
22 - 23	40.5	78.6	70.7
20 - 21	27.9	86.5	74.2
18 - 20	15.8	97.8	77.4

Overall accuracy of using age for determining GC/CT infections = 66.2% (95% CI 61.6- 70.7%)

ROC curve for performance of increasing age in determining GC/CT infections



A ROC curve demonstrates several things:

1. It shows the trade-off between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity).
2. The closer the curve follows the left-hand border and then the top border of the ROC space, the more accurate the test.
3. The closer the curve comes to the 45-degree diagonal of the ROC space, the less accurate the test.
4. The area under the curve is a measure of test accuracy.

B: SEXUAL ACTIVITY AS A CRITERION:

Sexual risk behaviour: The local NAS surveillance data[14] showed that condom use at the last sexual encounter showed no significant difference between the group infected with STIs (42.4%) *vs.* not infected with STIs (36.7%); Sexual partner from another province in the last 3 months showed no significant difference between the groups (11.6% vs. 9.3%); Sexual partner from another country in the last 3 months showed no significant difference (7.0% vs. 6.6%); History of any STI syndrome in last 12 months, 43% vs. 47%, respectively, no significant difference.

Rational antibiotic use: The National surveillance survey did not stratify according to recent sexual activity. (The GERMSA survey will hopefully provide such data in the near future). However, the PHC Committee was of the opinion that using a history of recent sexual activity (within the past 3 months as a criterion for including treatment for STI pathogens in the treatment regimen for women presenting with VDS was more logical and biologically plausible than the previous age criterion, and would probably avoid inappropriate over-treatment of VDS cases with azithromycin+ceftriaxone. Thus, the STG recommends history of recent sexual activity as the major criterion for presumptive STI treatment.

C: VDS ALGORITHMS DIFFERENTIATES CLINICALLY BETWEEN CANDIDIASIS ANDBACTERIAL VAGINOSIS:

Previous dual therapy (metronidazole+cotrimazole): In the 2014 PHC VDS algorithm women >35 years were treated with both clotrimazole and metronidazole to cover candidiasis, bacterial vaginosis and trichomonas. Clinical features of vaginal candidiasis were not included in the algorithm.

Co-infection: Co-infection with candida (CA) (necessitating clotrimazole treatment) and bacterial vaginosis (BV) (necessitating metronidazole treatment) is rare. In local surveillance data from the

[14]National Institute for Communicable Diseases. Report on the Sentinel Surveillance of Sexually Transmitted Infection Syndrome Aetiologies and HPV Genotypes among Patients attending Public Health Facilities in South Africa (April 2014 – September 2015), embargoed, to be published.

NAS study (2014-2015)[15], only 5% of patients (40/801 of VDS cases) had BV **plus** CA (without STI)."The negative association between BV and vulvovaginal candidiasis has been attributed to an alteration of vaginal pH in BV, which creates an unfavourable environment for candida colonization and co-infection".

D: SPECULUM EXAMINATION:
Speculum examination for all women presenting with VDS is recommended by the STI Programme[16] to differentiate between cervicitis and vaginitis, especially in sexually active women, to limit unnecessary treatment for gonorrhoea and chlamydia. Speculae are available at primary care level facilities. The PHC Committee was of the opinion that compulsory speculum examinations for all women presenting with VDS are probably not feasible. There is a note under both VDS algorithms that speculum examinations should be done in all cases, but lack of speculum examination does not preclude treatment. However, the PHC Committee recommended that speculum examination should be done if symptoms persist after treatment for BV, in order to identify those women who should receive STI treatment.

Recommendations:
A. Age be removed as a criterion for treating chlamydia and gonococcal infections versus bacterial vaginosis.
B. Sexual activity be added as a criterion for syndromic treatment of STI when presenting with VDS.
C. The VDS algorithm(s) differentiate clinically between candidiasis and bacterial vaginosis.
D. Speculum examination be included to distinguish between cervicitis and vaginitis, in those women with persistent symptoms after treatment for BV.

Rationale:
- Local surveillance data from the National Aetiological Surveillance (NAS) study (2014-2015) showed that age was not a good predictor of infection with STI pathogens in women with VDS. The survey did not ask women about sexual activity, so the sexual activity as a predictor could not be assessed. However, the PHC Committee was of the opinion that the latter criterion was more logical and biologically plausible.
- Local surveillance data from the NAS study (2014-2015) showed that of the 801 VDS cases, only 4.5% had STI and candidiasis co-infection.
- Speculum examination to distinguish vaginitis and cervicitis, may guide appropriate antibiotic treatment with metronidazole (7 day course) or ceftriaxone + azithromycin, respectively. Speculum examination is recommended in the NDoH STI Programme's Comprehensive STI Clinical Management Guidelines (currently in draft format).

Level of Evidence: III Surveillance data, Guidelines, Expert opinion.
Review indicator: New evidence of association between sexual activity and infection with STI pathogens in women presenting with VDS.

Fluconazole, oral*: not added*
fluconazole was not pragmatic for treating candidiasis that is not responsive to clotrimazole, topical/per vagina at primary level of care. Usage creep and hepatotoxicity associated with fluconazole are concerns.
Level of Evidence: III Expert opinion

Clotrimazole, topical: *added*
VDS algorithm recommends clotrimazole cream topically if prominent vulval symptoms are present (Clotrimazole, topical was in the 2008 VDS algorithm, removed from the 2014 version and recommended for re-inclusion in the updated VDS algorithm).
Level of Evidence: III Expert opinion

[15]National Institute for Communicable Diseases. Report on the Sentinel Surveillance of Sexually Transmitted Infection Syndrome Aetiologies and HPV Genotypes among Patients attending Public Health Facilities in South Africa (April 2014 – September 2015), embargoed, to be published.
[16]NDoH: Comprehensive STI Clinical Management Guidelines, draft version.

Referral

Recommendation: Patients failing treatment as indicated in the VDS algorithm must be referred. Their management to be included in the updated Adult Hospital Level STG.
Rationale: Specimens must be sent for specific antibiotic susceptibility tests at secondary level of care, if there is treatment failure at primary level of care.
Level of Evidence: III Expert opinion

12.2 LOWER ABDOMINAL PAIN (LAP)

Severely ill patients: Severe penicillin allergy
Gentamicin, IV: *not added*
Clindamycin, IV: *not added*
Ciprofloxacin, oral: *not added*
Ceftriaxone, IV, 1 g: *retained*
Metronidazole, oral, 400mg: *retained*

Gentamicin, IV, clindamycin, IV and ciprofloxacin, oral not recommended for severe penicillin allergic patients as a single dose prior to referral to secondary level of care.
Rationale: This is a single pre-referral dose and primary healthcare workers are trained in the management of anaphylaxis with relevant medicines available on emergency trolleys. Not pragmatic to add gentamicin IV, clindamycin, IV and ciprofloxacin, oral to the PHC EML for a single indication, which was possibly uncommon.
Level of Evidence: III Expert opinion

12.5 GENITAL ULCER SYNDROME (GUS)

Ceftriaxone, IM: *not added*
Limited evidence is available. A network meta-analysis of RCTs and observational studies[17] suggested that ceftriaxone may be effective as penicillin for treatment of syphilis (treatment failure of penicillin compared to ceftriaxone: RR 0.92, 95% CI 0.12 to 6.93, p= 0.992). However, this analysis was not powered to demonstrate equivalence (3 small RCTs with 30 participants in total were reviewed). Additional limitations included heterogeneity of studies: varied treatment regimens, different syphilis stages and outcomes (treatment failure vs reinfection). High-quality, large-scale RCTs are needed to verify the efficacy of ceftriaxone in treating early syphilis.
Recommendation: Ceftriaxone, IM, not be recommended for treatment of early syphilis.
Rationale: Insufficient evidence of efficacy for ceftriaxone to treat early syphilis.
Level of Evidence: II Systematic review of low quality studies

Benzathine benzylpenicillin, IM: *deleted*
Doxycyline, oral: *added*
Due to the global shortage of benzathine benzylpenicllin (limited global supply of the active pharmaceutical ingredient) doxycyline, oral is recommended for syndromic management of genital ulcers, except in pregnancy. Benzathine benzylpenicillin is the recommended treatment for syphilis in neonates and pregnant women. In pregnancy, azithromycin does not effectively treat syphilis in the foetus, and resistance develops rapidly to macrolides (e.g. azithromycin).
In addition, chancroid is not common.
Level of Evidence: III Guidelines[18]

[17] Liu HY, Han Y, Chen XS, Bai L, Guo SP, Li L, Wu P, Yin YP. Comparison of efficacy of treatments for early syphilis: A systematic review and network meta-analysis of randomized controlled trials and observational studies. PLoS One. 2017 Jun 28;12(6):e0180001.
[18] World Health Organization. WHO guidelines for the treatment of Treponema pallidum (syphilis), 2016. http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf

Pregnant women

Recommendation that pregnant women presenting with genital ulcer(s) in third trimester should be referred was included in the algorithm due to the risk of neonatal herpes, aligned with the NDoH Maternity Care Guidelines[19].

Level of Evidence: III Guidelines

Aciclovir-resistant ulcers

Azithromycin, oral, 1 g: *retained and directions for use amended*

Although, *Haemophilus ducreyi*is uncommon[20], the PHC ERC was of the opinion that presumptive treatment with azithromycin should be provided at PHC level of care, to cover the few cases that may occur. However, for pragmatic reasons, failure of azithromycin treatment requiring referral to secondary level of care for further pathology tests was amended from "*48 hours*" to "*7 days*".

Recommendation: Presumptive therapy for *Haemophilus ducreyii,* as single dose azithromycin be retained at primary level of care. Failure of therapy requiring referral to be assessed after 7 days, as oppose to 48 hours.

*Rationale: Haemophilus ducreyi*is uncommon, but presumptive therapy may cover the few cases that may present at primary level of care.

Level of Evidence: III Surveillance data, Expert opinion

NEMLC MEETING DISCUSSION: 2 NOVEMBER 2017

NEMLC Recommendations:

- GUS algorithm be updated replacing benzathine benzylpenicillin with doxycycline, except in pregnancy, due to the current global supply challenges.
- The foreword of the STI chapter provides information explaining the substitution of benzathine benzylpenicillin with doxycyline.
- The PHC Committee review the evidence for amoxicillin+probenicid for treatment of syphilis, for tabling at a follow-up NEMLC meeting.

12.6 BUBO

Azithromycin, oral, 1g: *dosing amended*

Azithromycin treatment amended for a period of 3 weeks, rather than 2 weeks as described in a surveillance study[21].Both recommendations are based on level 3 evidence; pharmacokinetic data and guidelines, respectively.

Recommendation: Update weekly azithromycin, 1 g, oral to a period of 3 weeks.

Rationale: Aligned with Infectious Diseases Society of America Guidelines: *Lymphogranuloma venereum* 2015: Clinical Presentation, Diagnosis, and Treatment.[22]

Level of Evidence: III Surveillance study, Guidelines

[19] NDoH Maternity Care Guidelines, 2016.

[20]González-Beiras C, Marks M, Chen CY, Roberts S, Mitjà O. Epidemiology of Haemophilus ducreyi Infections. Emerg Infect Dis. 2016 Jan;22(1):1-8

- *surveillance data reported 2 isolates of Haemophilus ducreyi and 1 isolate of Lymphogranuloma venereum (n=171specimens)*

[21]Hill SC, Hodson L, Smith A. An audit on the management of lymphogranuloma venereum in a sexual health clinic in London, UK.Int J STD AIDS. 2010 Nov;21(11):772-6.

[22] Stoner BP, Cohen SE. Lymphogranuloma Venereum 2015: Clinical Presentation, Diagnosis, and Treatment. Clin Infect Dis. 2015 Dec 15;61Suppl 8:S865-73.

12.7 BALANITIS/BALANOPOSTHITIS (BAL)

Benzathine benzylpenicillin, IM, 2.4MU: *deleted*
Syphilitic balanitis is very rare[23][24][25] and management with benzathine benzylpenicillin was removed from the BAL algorithm.
Recommendation: Benzathine benzylpenicillin removed from the BAL algorithm.
Rationale: Syphilitic balanitis reported to be rare.
Level of Evidence: III Guidelines[26]

12.8 SYPHILIS SEROLOGY AND TREATMENT

Early syphilis treatment
Doxycycline, oral: *amended to include indication "if benzathine benzylpenicillin is unavailable"*
Rationale: There is a continuous supply challenge with benzathine benzylpenicillin. Thus, use of this agent requires to be restricted further; as currently only this agent is available for use in syphilis in pregnancy. WHO guidelines for the treatment of *Treponema pallidum* (syphilis), 2016 recommends doxycycline as an alternative option.
Level of Evidence: III Guidelines[27]

Late latent syphilis treatment
Severe penicillin allergy or if benzathine benzylpenicillin is unavailable:
Doxycycline, oral: *added*
Rationale: Management in patients with severe penicillin allergy aligned with the WHO guidelines for the treatment of *Treponema pallidum* (syphilis), 2016.
Level of Evidence: III Guidelines[28]

Pregnant women
Amoxicillin, oral: *added*
Probenicid, oral: *added*
Refer to the medicine review: Amoxicillin + probenecid for syphilis in pregnant women, January 2018, for detailed information.

Amoxicillin+Proben
icid_Syphilis in preg

Recommendation: The Primary Health Care Committee recommended that amoxicillin plus probenecid to be included as an alternative if benzathine penicillin unavailable, for treatment of syphilis in pregnancy. RPR follow up recommended for all patients treated with this regimen, as tolerability and adherence may be problematic and there is little published data in pregnancy with this regimen.
Rationale: Due to long-term supply challenges of benzathine penicillin, doxycycline, an alternative option, should be avoided in pregnancy. A retrospective observational study[29] showed that

[23] - Abdennader S, Janier M, Morel P. Syphilitic balanitis of Follmann: three case reports. Acta DermVenereol. 2011 Mar;91(2):191-2.
[24]Mainetti C, Scolari F, Lautenschlager S. The clinical spectrum of syphilitic balanitis of Follmann: report of five cases and a review of the literature. J EurAcadDermatolVenereol. 2016 Oct;30(10):1810-1813.
[25]Korta DZ, Lewin JM, Patel RR, Sanchez M. Acute Syphilitic Balanitis and Gross Penile Edema in an HIVInfected Man. Global Journal of Dermatology & Venereology. 2013;1:18-20.
[26]Edwards SK, Bunker CB, Ziller F, van der Meijden WI.2013 European guideline for the management of balanoposthitis.Int J STD AIDS. 2014 Aug;25(9):615-26.
[27]World Health Organization. WHO guidelines for the treatment of Treponema pallidum (syphilis), 2016. http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf
[28]World Health Organization. WHO guidelines for the treatment of Treponema pallidum (syphilis), 2016. http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf

amoxicillin+probenecid was effective in treating syphilis, with a 4-fold decrease in RPR titer reduction compared to no treatment.

Level of Evidence: III Observational Strudy

NEMLC MEETING DISCUSSION, 1 FEBRUARY 2018:

- **Amoxicillin + probenecid:**
  Pragmatic implications: The NEMLC was of the opinion that stocking probenecid at every PHC facility in the event that benzathine benzylpenicllin was unavailable (through normal procurement processes or S21 approval) was not considered to be pragmatic.
  NEMLC Recommendation: Prescribing of amoxicillin + probenecid for management of syphilis in pregnant women, when there is a stock-out of benzathine benzylpenicillin be restricted to doctors only (thereby limiting the number of facilities that could access amoxicillin + probenecid).
  Rationale: Limited indication of amoxicillin + probenecid for management of syphilis in pregnant women, when there is a stock-out of benzathine benzylpenicillin warrants restrictive measures to prevent wastage.
  Level of Evidence: III Expert opinion

Syphilis serology

RPR testing: *amended*

Evidence suggests that doxycyline is as efficacious as benzathine penicillin for the treatment of early syphilis, and there is no significant difference in treatment outcomes. [30] [31] [32]Therefore, monitoring for RPR serological response is unnecessary in doxycycline-treated patients. Testing for serological response in early syphilis should be done at least 6 months after appropriate therapy, therefore long-term follow-up of RPR is impractical at primary level.

Recommendation: Follow-up RPR testing 6 months after doxycycline treatment removed form syphilis treatment algorithm.

Rationale: Serological response rate of doxcycyline shown to be comparable to penicillin for the management of early syphilis.

Level of Evidence: II Systematic review of RCTS and observational studies, Observational studies, Expert opinion

NEMLC MEETING DISCUSSION, 1 FEBRUARY 2018:

- **Amoxicillin + probenecid:**
  Pragmatic implications: The NEMLC was of the opinion that stocking probenecid at every PHC facility in the event that benzathine benzylpenicllin was unavailable (through normal procurement processes or S21 approval) was not considered to be pragmatic.
  NEMLC Recommendation: Prescribing of amoxicillin + probenecid for management of syphilis in pregnant women, when there is a stock-out of benzathine benzylpenicillin be restricted to doctors only (thereby limiting the number of facilities that could access amoxicillin + probenecid).
  Rationale: Limited indication of amoxicillin + probenecid for management of syphilis in pregnant women, when there is a stock-out of benzathine benzylpenicillin warrants restrictive measures to prevent wastage.
  Level of Evidence: III Expert opinion

[29] Tanizaki R, Nishijima T, Aoki T, Teruya K, Kikuchi Y, Oka S, et al. High-dose oral amoxicillin plus probenecid is highly effective for syphilis in patients with HIV infection. Clin Infect Dis. 2015;61(2):177-83. https://www.ncbi.nlm.nih.gov/pubmed/25829004

[30] Liu HY, Han Y, Chen XS, Bai L, Guo SP, Li L, Wu P, Yin YP. Comparison of efficacy of treatments for early syphilis: A systematic review and network meta-analysis of randomized controlled trials and observational studies. PLoS One. 2017 Jun 28;12(6):e0180001. https://www.ncbi.nlm.nih.gov/pubmed/28658325

[31] Salado-Rasmussen K, Hoffmann S, Cowan S, Jensen JS, Benfield T, Gerstoft J, Katzenstein TL. Serological Response to Treatment of Syphilis with Doxycycline Compared with Penicillin in HIV-infected Individuals. Acta Derm Venereol. 2016 Aug 23;96(6):807-11. https://www.ncbi.nlm.nih.gov/pubmed/26568359

[32] Dai T, Qu R, Liu J, Zhou P, Wang Q. Efficacy of Doxycycline in the Treatment of Syphilis. Antimicrob Agents Chemother. 2016 Dec 27;61(1). pii: e01092-16. https://www.ncbi.nlm.nih.gov/pubmed/27795370

12.10 TREATMENT OF PARTNERS

Ceftriaxone, 250 mg, IM: *added*
Azithromycin, 1 g, oral: *added*
Metronidazole, 2g, oral: *added*
Doxycyline, oral: *added*
Benzathine benzylpenicillin, IM 2.4MU: *added*
Lidocaine 1% without epinephrine (adrenaline): *added*

The following treatment regimens were included in the STI chapter for treatment of partners (refer to the STI chapter for detailed information).

Syndrome	Asymptomatic Partner	Symptomatic partner
VDS	Ceftriaxone + azithromycin + metronidazole	Ceftriaxone + azithromycin + metronidazole PLUS treatment for syndrome present if not included in the above
LAP	Ceftriaxone + azithromycin + metronidazole	Ceftriaxone + azithromycin + metronidazole PLUS treatment for syndrome present if not included in the above
MUS	Ceftriaxone + azithromycin	Ceftriaxone + azithromycin PLUS treatment for syndrome present if not included in the above
Scrotal swelling	Ceftriaxone + azithromycin	Ceftriaxone + azithromycin PLUS treatment for syndrome present if not included in the above
GUS	Benzathine penicillin	Doxycycline/benzathine penicillin PLUS treatment for syndrome present if not included in the above
Bubo	Azithromycin	Azithromycin PLUS treatment for syndrome present if not included in the above

Aligned with the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines, 2015[33].
Level of Evidence: III Guidelines

12.13 PUBIC LICE (PL)

Pediculosis of the eyelashes or eyebrows
Yellow petroleum jelly: *added*
White petroleum jelly: *not added*
White petroleum jelly should not be used near the eyes.
Level of Evidence: III Expert opinion

2024 Updates following the publication of the chapter
Historical global shortages of benzathine benzylpenicillin led to the STGs amendment to prioritise the limited supply of benzathine benzylpenicillin for the treatment of syphilis for pregnant women and children. In May 2024 (see published NDoH circular ref:2024/05/30/EDP/01) there was an indication that the national supply of benzathine benzylpenicillin injection has stabilized and therefore the STG recommendation to restrict the use of benzathine benzylpenicillin injection to only pregnant women was amended as follows:

[33]Centers for Disease Control and Prevention. 2015 Sexually Transmitted Diseases Treatment Guidelines. https://www.cdc.gov/std/tg2015/

Benzathine benzylpenicillin

Benzathine benzylpenicillin remains the recommended treatment for syphilis. Azithromycin is not recommended for the treatment of syphilis in pregnancy as azithromycin does not effectively treat syphilis in the fetus, and resistance develops rapidly to macrolides. Therefore, benzathine benzylpenicillin should be reserved for use in pregnant women and children during times of a confirmed stock shortage.