

CHAPTER 26

SEXUALLY TRANSMITTED INFECTIONS

SEXUALLY TRANSMITTED INFECTIONS MANAGED AT SECONDARY LEVEL OF CARE

These guidelines apply to patients who are referred from primary healthcare centres for further investigation and management of **persistent** STI symptoms or syndromes that have not improved or resolved and are still present 7 days after administration of standard first-line syndromic therapy.

26.1 MALE URETHRITIS SYNDROME (MUS)

A64 + N34.1

Male urethritis/ visible urethral discharge that persists despite appropriate syndromic management should be investigated for suspected ceftriaxone-resistant gonorrhea. Referral letter from PHC should include all relevant information (including HIV status, treatment history and partner notification and management).

INVESTIGATIONS

- » It is essential to confirm ceftriaxone-resistant gonorrhea.
- » All NHLS standard laboratory forms must include the following information:
 - Name and contact details (cellphone number + email address) of requesting healthcare worker.
- » Genital specimen collection and test requests (to confirm presence of any STI pathogens and if *Neisseria gonorrhoeae* present, and determine ceftriaxone susceptibility):
 - **Materials:** Two Dacron swabs (wire shaft, slender tip); Amies transport medium (all obtained from local NHLS laboratory).
 - > Urethral swab 1: Gently insert 2cm into the urethral meatus, and rotate for 5-10 seconds. Place this swab immediately into Amies transport medium.
 - > Test request: Transport on ice to local NHLS laboratory as soon as possible, preferably within 24 hours for *Neisseria gonorrhoeae* culture and sensitivity testing. (Contact laboratory for directions on transport of specimens).
 - > Presumptive diagnosis: Persistent urethritis due to possible ceftriaxone-resistant gonorrhea.
 - > Urethral swab 2: Gently insert 2cm into urethral meatus, and rotate for 5-10 seconds. Place in a sterile universal container or tube, cut off the wire shaft and close the container.
 - > Test request: transport on ice to NICD STI reference laboratory as soon as possible for PCR genital discharge pathogens.

- > Presumptive diagnosis: Persistent urethritis due to possible ceftriaxone-resistant gonorrhea.

MEDICINE TREATMENT

Persistent urethral discharge after 7 days confirmed on examination, pending results:

- Ceftriaxone, IM, 1 000 mg immediately as a single dose.
 - Dissolve ceftriaxone 1 g in 3.6 mL lidocaine 1% without adrenaline (epinephrine).

LoE: IIIⁱ

AND

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

LoE: IIIⁱⁱ

LoE: IIIⁱⁱⁱ

Severe penicillin allergy: Z88.0

- Gentamicin, IM, 6 mg/kg, IM as a single dose. (See Appendix II for guidance on prescribing).

AND

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

LoE: III^{iv}

Ask patient to return in two weeks for follow-up of laboratory results and further clinical evaluation. Treat accordingly.

26.2 VAGINAL DISCHARGE SYNDROME (VDS)

B37.3/N76.0/N89.8

Abnormal vaginal discharge that persists despite appropriate syndromic management should be investigated. Referral letter from PHC should include all relevant information (including HIV status, treatment history and partner notification and management).

INVESTIGATIONS

- » All NHLS standard laboratory forms must include the following information:
 - Name and contact details (cellphone number + email address) of requesting healthcare worker.
- » Genital specimen collection and test requests (to confirm presence of STI pathogens and if *Neisseria gonorrhoeae* is present, and determine ceftriaxone susceptibility):
 - *Materials:* One cotton-tip swab (plastic shaft); two Dacron swabs (plastic shaft, slender tip); Amies transport medium (all obtained from local NHLS laboratory). Insert speculum to visualize cervix.
 - *Endocervical swab 1:* Gently insert Dacron swab 2cm into the endocervical canal, and rotate for 5-10 seconds. Place this swab immediately into Amies transport medium.
 - > *Test request:* Transport on ice to local NHLS laboratory as soon as possible, preferably within 24 hours for *Neisseria gonorrhoeae* culture & sensitivity testing.

- > *Presumptive diagnosis*: Persistent cervicitis due to possible ceftriaxone-resistant gonorrhea.
- *Endocervical swab 2*: Gently insert Dacron swab 2cm into the endocervical canal, and rotate for 5-10 seconds. Place in sterile universal container or tube, break off plastic shaft and close the container.
 - > *Test request*: Transport on ice to NICD STI Reference laboratory as soon as possible for PCR genital discharge pathogens.
 - > *Presumptive diagnosis*: Persistent cervicitis/vaginal discharge due to possible ceftriaxone-resistant gonorrhea.
- *Vaginal swab1*: Gently insert cotton-tip swab into the vagina and then dip swab in the poster fornix fluid. Place swab in sterile universal container or tube, break off plastic shaft and close the container.
 - > *Test request*: Transport to local NHLS laboratory as soon as possible for M/C/S - for bacterial vaginosis; *Candida* culture and sensitivity testing.
 - > *Presumptive diagnosis*: Persistent vaginal discharge due to bacterial vaginosis or candidiasis.

MEDICINE TREATMENT

Persistent cervicitis confirmed on speculum examination, pending results:

- Ceftriaxone, IM, 1 g immediately as a single dose.
 - Dissolve ceftriaxone 1 g in 3.6 mL lidocaine 1% without adrenaline (epinephrine).

LoE: III^v

AND

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

LoE: III^{vi}

If metronidazole, oral was not given at PHC prior to referral administer:

- Metronidazole, oral, 2 g as a single dose.

LoE: III^{vii}

Severe penicillin allergy: Z88.0

- Gentamicin, IM, 6 mg/kg, IM as a single dose. (See Appendix II for guidance on prescribing).

AND

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

LoE: III^{viii}

If metronidazole, oral was not given at PHC prior to referral administer:

- Metronidazole, oral, 2 g as a single dose.

LoE: III^{ix}

Ask patient to return in two weeks for follow-up of laboratory results and further clinical evaluation. Treat accordingly.

26.3 GENITAL ULCER SYNDROME (GUS)

A60.9/A51.0

Genital ulcer disease that persists despite appropriate syndromic management

should be investigated. Referral letter from PHC should include all relevant information (including HIV status, treatment history and partner notification and management).

INVESTIGATIONS

- » All NHLS standard laboratory forms must include the following information:
 - Name and contact details (cellphone number + email address) of requesting healthcare worker.
- » Genital specimen collection and test requests:
 - Materials: Two cotton-tip swabs (plastic shaft); one Dacron swab (wire shaft); glass slide, slide box (all obtained from local NHLS laboratory)
 - Cotton swab 1: Prior to taking specimen, roll a cotton-tip swab across the lesion gently to remove exudates from secondary infection and/ or debris in a way that minimizes bleeding. Discard cotton swab.
 - Cotton swab 2: Roll a second cotton-tip swab over the base of the ulcer, including the ulcer edges. Make a thin smear by rolling evenly over the centre of a labelled-glass slide to the size of a R2 coin. Air dry slide and place in slide box. Discard cotton swab.
 - Dacron swab: Collect material from base of ulcer lesion; place swab in sterile universal container or tube and cut off wire shaft. Close container.
 - > *Test request:* Transport glass slide and Dacron swab on ice to NICD STI Reference laboratory as soon as possible for microscopy for Donovanosis and PCR genital ulcer pathogens.
 - > *Presumptive diagnosis:* Persistent genital ulcer disease
- » Venous blood specimen: 5 mL in serum separator tube for syphilis serology – send to local NHLS laboratory.

MEDICINE TREATMENT

Ask patient to return in two weeks for follow-up of laboratory results and further clinical evaluation. Treat accordingly, but note that syphilis does not require re-treatment if benzathine penicillin was used to treat GUS.

If the syndromic treatment at PHC used doxycycline instead of benzathine penicillin and syphilis is detected on PCR, treat with:

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

LoE: III^x

Recurrent herpes

For frequent recurrences of herpes simplex (i.e. ≥4 episodes of clinically apparent reactivations per year), suppressive antiviral therapy may be considered.

- Antiviral (active against herpes simplex) e.g.:
 - Aciclovir, oral, 400 mg 12 hourly.
 - Review annually for ongoing suppressive therapy.

LoE: II^{xi}

LoE: III^{xii}

REFERRAL

If ulcer PCR results for STI pathogens are inconclusive and genital ulceration persists, refer to specialist for genital ulcer biopsy and histopathological examination to exclude a non-infectious cause, which includes cancer.

26.4 BUBO

A58

Buboes that persist despite appropriate syndromic management should be investigated. Referral letter from PHC should include all relevant information (i.e. HIV status, treatment history and partner notification and management).

INVESTIGATIONS

- » All NHLS standard laboratory forms must include the following information:
 - Name and contact details (cellphone number + email address) of requesting healthcare worker.
- » Genital specimen collection and test requests:

Materials: One Dacron swab (wire shaft); 21-gauge sterile needle and syringe; two sterile universal containers or tubes (all obtained from local NHLS laboratory).

 1. If genital ulcer is present:
 - Dacron swab: Collect material from base of ulcer lesion; place swab in sterile universal container or tube and cut off wire shaft. Close container.
 - > *Test request:* Transport Dacron swab on ice to NICD STI reference laboratory as soon as possible for PCR for chancroid and LGV.
 2. If genital ulcer is absent:
 - After topical disinfection, insert 21-gauge needle into bubo and aspirate pus into syringe. Transport pus in two sterile tubes/ containers to laboratory.
 - > *Test request:* send one tube on ice to NICD STI reference laboratory as soon as possible for PCR for chancroid and Lymphogranuloma Venereum (LGV).
 - > *Test request:* send one tube to local NHLS laboratory for bacterial M/C/S.
 - Presumptive diagnosis: Persistent bubo unresponsive to syndromic management.

MEDICINE TREATMENT

- Doxycycline 100 mg, oral 12 hourly for 21 days.

LoE: III^{xiii}

Note: Follow-up until there is complete resolution of symptoms.

Fluctuant buboes may require frequent needle aspiration to prevent rupture – review every 72 hours, as necessary.

For laboratory-confirmed diagnosis of LGV:

- Doxycycline 100 mg, oral 12 hourly for more than 21 days may be required for complete resolution of disease.

LoE: III^{xiv}**References:**

- ⁱ Ceftriaxone (1000mg - MUS): Fifer H, Natarajan U, Jones L, Alexander S, Hughes G, Golparian D, Unemo M. Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea. NEJM 2016. 374;25: 2504-2506.
- Ceftriaxone (1000mg - MUS): Bignell C, Unemo M; European STI Guidelines Editorial Board. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. Int J STD AIDS. 2013 Feb;24(2):85-92. <https://www.ncbi.nlm.nih.gov/pubmed/24400344>
- ⁱⁱ Lidocaine 1%: MCC registered package inserts of Koce® 250 mg, 500 mg, 1 g; Rociject® 500 mg, 1 g; Ofraamax® 250 mg, 1 g.
- ⁱⁱⁱ Azithromycin (2000mg - MUS): Bignell C, Unemo M; European STI Guidelines Editorial Board. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. Int J STD AIDS. 2013 Feb;24(2):85-92. <https://www.ncbi.nlm.nih.gov/pubmed/24400344>
- ^{iv} Gentamicin, IM + azithromycin, oral: Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. <https://www.ncbi.nlm.nih.gov/pubmed/26042815>
- ^v Ceftriaxone, IM + azithromycin: World Health Organisation: WHO guidelines for the treatment of *Neisseria gonorrhoeae*, 2016. <http://apps.who.int/iris/bitstream/10665/246114/1/9789241549691-eng.pdf>
- ^{vi} Lidocaine 1%: MCC registered package inserts of Koce® 250 mg, 500 mg, 1 g; Rociject® 500 mg, 1 g; Ofraamax® 250 mg, 1 g.
- ^{vii} Metronidazole: Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. <https://www.ncbi.nlm.nih.gov/pubmed/26042815>
- ^{viii} Gentamicin, IM + azithromycin, oral: Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. <https://www.ncbi.nlm.nih.gov/pubmed/26042815>
- ^{ix} Metronidazole: Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. <https://www.ncbi.nlm.nih.gov/pubmed/26042815>
- ^x Benzathine benzylpenicillin (GUS): World Health Organization. ^{ix} WHO guidelines for the treatment of *Treponema pallidum* (syphilis), 2016. <http://www.who.int/reproductivehealth/publications/rts/syphilis-treatment-guidelines/en/>
- ^{xi} Antiviral therapy, oral (recurrent herpes simplex): Le Cleach L, Trinquart L, Do G, Maruani A, Lebrun-Vignes B, Ravaut P, Chosidow O. Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients. Cochrane Database Syst Rev. 2014 Aug 3;(8):CD009036. <https://www.ncbi.nlm.nih.gov/pubmed/25086573>
- ^{xii} Antiviral therapy, oral (recurrent herpes simplex): Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. <https://www.ncbi.nlm.nih.gov/pubmed/26042815>
- Aciclovir, oral: Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. <https://www.ncbi.nlm.nih.gov/pubmed/26042815>
- ^{xiii} Doxycycline (21 days: Bubo): de Vries HJ, Smelov V, Middelburg JG, Pleijster J, Speksnijder AG, Morré SA. Delayed microbial cure of lymphogranuloma venereum proctitis with doxycycline treatment. Clin Infect Dis. 2009 Mar 1;48(5):e53-6. <https://www.ncbi.nlm.nih.gov/pubmed/19191633>
- ^{xiv} Doxycycline (> 21 days: Bubo): Oud EV, de Vrieze NH, de Meij A, de Vries HJ. Pitfalls in the diagnosis and management of inguinal lymphogranuloma venereum: important lessons from a case series. Sex Transm Infect. 2014 Jun;90(4):279-82. <https://www.ncbi.nlm.nih.gov/pubmed/24787368>

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 26: SEXUALLY TRANSMITTED INFECTIONS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Background: The chapter was developed to provide guidance for sexually transmitted infection (STI) cases that are not responding to primary treatment at primary health care (PHC) facilities (described in the PHC STI chapter), for further investigation and management. Guidance is likewise provided regarding collection of specimens that must be sent for specific antibiotic susceptibility tests.

Management of STIs at secondary level of care is only for treatment of resistant cases, referred from primary level of care (where syndromic management takes place). Empiric antibiotics are recommended for cases referred from primary level of care and presumptuous treatment continued, whilst specimens are submitted for testing. Thereafter, treatment is guided by laboratory results.

Resistance: NEMLC recommended that a note (in a box) to be added emphasising that cephalosporin resistance to be clearly documented in the light of global gonorrhoea microbial resistance.

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the chapter for sexually transmitted infections chapter.

SECTION	MEDICINE	ADDED/DELETED/AMENDED
25.1 Male urethritis syndrome (MUS) - Treatment failure cases referred from PHC level - Severe penicillin allergy	Ceftriaxone, IM, 1 g	Added
	Lidocaine 1%	Added
	Azithromycin, oral, 2 g	Added
	Gentamicin, IM	Added
	Azithromycin, oral, 2g	Added
25.2 Vaginal discharge syndrome (VDS) - Treatment failure of cervicitis cases referred from PHC level - Severe penicillin allergy	Ceftriaxone, IM, 1 g	Added
	Lidocaine 1%	Added
	Azithromycin, oral, 2 g	Added
	Metronidazole, oral, 2 g	Added, if not administered at PHC level
	Gentamicin, IM	Added
25.3 Genital ulcer syndrome (GUS) - Syphilis confirmed and previous treatment with doxycycline at PHC - Syphilis confirmed and severe penicillin allergy in pregnancy - recurrent herpes simplex	Azithromycin, oral, 2	Added
	Metronidazole, oral, 2 g	Added, if not administered at PHC level
	Benzathine benzylpenicillin, IM	Added
	Macrolides	Not added (penicillin desensitisation recommended)
	Antivirals for herpes simplex	Added
25.4 Bubo - Treatment failure of bubo cases referred from PHC level	Aciclovir, oral	Added as example of class
	Doxycycline, oral	Added

Note: Dr Kularatne from the National Institute of Communicable Diseases provided support to develop this chapter.

25.1 MALE URETHRITIS SYNDROME (MUS)

Treatment failure cases referred from PHC level:

Ceftriaxone, IM, 1 g: added

Lidocaine 1%: added

Azithromycin, oral, 2 g: added

Severe penicillin allergy:

Gentamicin, IM: added

Azithromycin, oral, 2g: added

Gentamicin: There are no established clinical breakpoints that have been determined by CLSI EUCAST for gentamicin. Therefore, MICs from Malawi are being used as gentamicin is being used as 1st line therapy for syndromic management of MUS. Malawian cut-off for susceptible pathogens tentatively given as ≤ 4 with intermediate resistance having a MIC of 8 to 16 and resistant pathogens a MIC > 32 .^{1 2} Local NICD data that is currently being analysed shows intermediate resistance to gentamicin, but there is no evidence that this translates into clinical failure. The 2014 susceptibility data showed intermediate resistance for gentamicin in 83 % (53 isolates tested)³.

Guidelines:

- *WHO Guidelines* (2016) recommends dual therapy for the treatment of *Neisseria gonorrhoeae*⁴: "ceftriaxone 500 mg, IM + azithromycin 2g, oral" or "gentamicin 240 mg, IM + azithromycin 2 g, oral" or "spectinomycin 2 g, IM + azithromycin 2 g, oral". Although the MIC for spectinomycin is low with no resistant isolates reported to date, spectinomycin is not available on the South African market.
- *CDC Guidelines* (2015)⁵ recommends, "gentamicin 240 mg + azithromycin 2g".
- *European guidelines*⁶ recommends 1 g dose of ceftriaxone as part of dual therapy when cephalosporin resistance has been identified.

Isolated cases of emergence of multi-drug and extensively-drug resistant gonorrhoea have been reported. Case of pharyngeal gonorrhoea resistant to "ceftriaxone 500 mg + azithromycin 1 g", successfully treated with higher dose "ceftriaxone 1 g + azithromycin 2g" was reported⁷.

Recommendations:

- Ceftriaxone, IM 1 g dose as part of dual therapy with azithromycin 2 g for MUS cases unresponsive to the lower dose of ceftriaxone 250 mg.

Rationale: Aligned with guideline recommendations.

Level of Evidence: III Guidelines

- *Severe penicillin allergy:* Gentamicin 6mg/kg and azithromycin, oral, 2g as part of dual therapy for MUS cases unresponsive to azithromycin, oral, 2 g.

Rationale: Aligned with the CDC STI Guidelines, 2015⁸.

Level of Evidence: III Guidelines

¹ - Bala M, Singh V, Philipova I, Bhargava A, Chandra Joshi N, Unemo M. Gentamicin in vitro activity and tentative gentamicin interpretation criteria for the CLSI and calibrated dichotomous sensitivity disc diffusion methods for *Neisseria gonorrhoeae*. J Antimicrob Chemother. 2016 Jul;71(7):1856-9.

² Brown LB, Krysiak R, Kamanga G, Mapanje C, Kanyamula H, Banda B, Mhango C, Hoffman M, Kamwendo D, Hobbs M, Hosseinipour MC, Martinson F, Cohen MS, Hoffman IF. *Neisseria gonorrhoeae* antimicrobial susceptibility in Lilongwe, Malawi, 2007. Sex Transm Dis. 2010 Mar;37(3):169-72.

³ - NICD: Report on the Sentinel Surveillance of Sexually Transmitted Infection Syndrome Aetiologies and HPV Genotypes among Patients attending Public Health Facilities in South Africa, draft version, 4 November 2016.

- NICD susceptibility data (*N.gonorrhoeae* /gentamicin) data for Gauteng region on file.

⁴WHO Guidelines for the treatment of *Neisseria gonorrhoeae*, 2016. <http://www.who.int/reproductivehealth/publications/rtis/gonorrhoea-treatment-guidelines/en/>

- Note: the cited systematic review in the WHO 2016 guidelines conclusion: "Gentamicin does not meet current CDC criteria for recommended treatment of gonorrhoea. However, if cephalosporin resistance emerges, gentamicin may be a useful alternative agent. Evaluation of additional regimens, including combination therapy, is warranted".

⁵ Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. <https://www.ncbi.nlm.nih.gov/pubmed/26042815>

⁶ Bignell C, Unemo M; European STI Guidelines Editorial Board. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. Int J STD AIDS. 2013 Feb;24(2):85-92.

⁷ Fifer H, Natarajan U, Jones L, Alexander S, Hughes G, Golparian D, Unemo M. Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea. N Engl J Med. 2016 Jun 23;374(25):2504-6. <https://www.ncbi.nlm.nih.gov/pubmed/27332921>

⁸ Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. <https://www.ncbi.nlm.nih.gov/pubmed/26042815>

25.2 VAGINAL DISCHARGE SYNDROME (VDS)

Treatment failure of cervicitis cases referred from PHC level:

Ceftriaxone, IM, 1 g: *added*

Lidocaine 1%: *added*

Azithromycin, oral, 2 g: *added*

Metronidazole, oral, 2 g: *added, if not administered at PHC level*

Severe penicillin allergy:

Gentamicin, IM: *added*

Azithromycin, oral, 2g: *added*

Metronidazole, oral, 2 g: *added, if not administered at PHC level*

*Dual therapy: Treatment of resistant *Neisseria gonorrhoeae* aligned with Guideline recommendations.*

Level of Evidence: III Guidelines

Metronidazole:

Recommendation: An immediate single dose of metronidazole not be routinely recommended with dual therapy (ceftriaxone/gentamicin + azithromycin) in cases of persistent cervicitis, unresponsive to initial treatment of ceftriaxone, azithromycin, metronidazole with follow on treatment with a prolonged course of metronidazole for treatment of Trichomonas and bacterial vaginosis.

Rationale: Persistent cases of cervicitis would have probably been treated with single dose as well as a 7-day course of metronidazole at primary level of care prior to referral. Aligned with CDC STI Guidelines (2015).

Level of Evidence: III Guidelines⁹

25.3 GENITAL ULCER SYNDROME (GUS)

Syphilis confirmed:

Benzathine benzylpenicillin, IM: *added*

Practical guidance has been provided to treat patients previously treated with 14-day course of doxycycline at PHC (with the possibility of non-adherence) with benzathine benzylpenicillin for confirmed syphilis. Of note is that there has been continuous supply challenges of benzathine benzylpenicillin globally, and this medicine has routinely been accessed through the section 21 application process.

Aligned with WHO guidelines for the treatment of *Treponema pallidum* (syphilis), 2016¹⁰; and

Level of Evidence: III Guidelines, Expert opinion

Syphilis confirmed and severe penicillin allergy in pregnancy:

Macrolides, oral: *not added*

Penicillin desensitisation is recommended for confirmed maternal syphilis in severe penicillin allergy.

Although the WHO syphilis guideline (2016) recommends macrolides when penicillin is not available, the Adult Hospital Level Committee was of the opinion that macrolides not be recommended as the medicine does not cross the blood brain barrier and not advisable for latent syphilis (maternal syphilis).

Level of Evidence: III Expert opinion

Recurrent herpes

Antivirals for herpes simplex: *added as a therapeutic class*

Aciclovir, oral: *added as an example of class (listed in the STG)*

Valaciclovir, oral: *added as an example of class (therapeutic interchange database)*

Famciclovir, oral: *added as an example of class (therapeutic interchange database)*

⁹ Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924

¹⁰ 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>

Aciclovir, oral: The dosing regimen for aciclovir was sourced from the CDC STI Guidelines, and the comparable prices of the various antiviral agents derived from work that was previously done by the PHC Committee, though for herpes zoster and herpes zoster¹¹ – aciclovir is still the more affordable option.

Recommendation: Aciclovir, oral 400 mg 12 hourly be recommended as an example of antivirals for laboratory-confirmed herpes simplex, with annual review for evaluation for continued suppressive therapy.

Rationale: Systematic review of low quality RCTs suggests that suppressive antiviral therapy with either aciclovir, valaciclovir or famciclovir in (immunocompetent and non-pregnant) patients experiencing at least four recurrences of genital herpes per year decreased the number of patients with at least one recurrence vs placebo¹². Furthermore, Network meta-analysis was underpowered to show superiority of one medicine over another. Aciclovir is the more affordable option and dosing aligned to Centers for Disease Control and Prevention, Sexually transmitted diseases treatment guidelines, 2015 that informed presumptive therapy recommendations in the PHC STGs and EML, 2018.

Level of Evidence: II Systematic review of RCTs of low methodological quality¹², Guidelines¹³

Going forward: NEMLC recommended that the forthcoming evidence (GERMS-SA data from NICD) for the presumptive use of aciclovir for GUS amongst the HIV-uninfected be reviewed in the next review cycle.

25.4 BUBO

Treatment failure of bubo cases referred from PHC level:

Doxycycline, oral, 100 mg: added

Study¹⁴ suggests that "delayed microbial cure of LGV proctitis should be considered in improved treatment regimens". Recommendation of 21-day doxycycline regimen for LGV proctitis aligned with CDC STI Guidelines (2015)¹⁵.

Rationale: Aligned with Guidelines

Level of Evidence: III Guidelines

Prolonged course of doxycycline (>21 days) recommended for complete resolution of disease, if necessary, as described in a case series¹⁶.

Level of Evidence: III Case series

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)

- **Note:** Information was sourced from NEMLC ratified minutes and NEMLC-approved documents.

¹¹ Aciclovir 400 mg 12 hourly = R1.27/day (Contract circular RT301-2017)

Famciclovir 250 mg 12 hourly = R33.40/day (60% of average SEP 22 October 2018 SEP database)

Valaciclovir 1 g daily = R21.39/day (60% of average SEP 22 October 2018 SEP database)

¹² Le Cleach L, Trinquart L, Do G, Maruani A, Lebrun-Vignes B, Ravaud P, Chosidow O. Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients. Cochrane Database Syst Rev. 2014 Aug 3;(8):CD009036. <https://www.ncbi.nlm.nih.gov/pubmed/25086573>

¹³ Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. <https://www.ncbi.nlm.nih.gov/pubmed/26042815>

¹⁴ de Vries HJ, Smelov V, Middelburg JG, Pleijster J, Speksnijder AG, Morré SA. Delayed microbial cure of lymphogranuloma venereum proctitis with doxycycline treatment. Clin Infect Dis. 2009 Mar 1;48(5):e53-6. <https://www.ncbi.nlm.nih.gov/pubmed/19191633>

¹⁵ Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. <https://www.ncbi.nlm.nih.gov/pubmed/26042815>

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