SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 25: 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*	Ceftriaxone, IM, 1 g	Added
	Lidocaine 1%	Added
	Azithromycin, oral, 2 g	Added
- *Severe penicillin allergy*	Gentamicin, IM	Added
	Azithromycin, oral, 2g	Added
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, 2	Added
	Metronidazole, oral, 2 g	Added, if not administered at PHC level
25.3 Genital ulcer syndrome (GUS) - *Syphilis confirmed and previous treatment with doxycycline at PHC*	Benzathine benzylpenicillin, IM	Added
- *Syphilis confirmed and severe penicillin allergy in pregnancy*	Macrolides	Not added (penicillin desensitisation recommended)
- *recurrent herpes simplex*	Antivirals for herpes simplex	Added
	Aciclovir, oral	Added as example of class
25.4 Bubo - *Treatment failure of bubo cases referred from PHC level*	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 reported[7].

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, 2015[8].
  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, drfat version, 4 November 2016.
- NICD susceptibility data (N.gonorrhoeae /gentamicin) data for Gauteng region on file.
[4]WHO 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 ceftriaxine, 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 Guidelines[9]

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), 2016[10]; 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 zoster[11] – 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 placebo". 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 quality [12], Guidelines[13]

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*
Study[14] 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 doxycyline (>21 days) recommended for complete resolution of disease, if necessary, as described in a case series[16].
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
[16] 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