**PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST**

**CHAPTER 12: SEXUALLY TRANSMITTED INFECTIONS**

**RECCOMMENDATIONS FROM THE NEMLC MEETING: 2 NOVEMBER 2017**

**Medicine amendment recommendations, following initial review of the chapter, are listed below. Kindly review the medicine amendments in the context of the chapter.**

**AMENDMENTS:**

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| **SECTION** | **MEDICINE/MANAEGEMENT** | **ADDED/DELETED/AMENDED** |
| **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 |
| **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 |
| 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)** | Benzathine benzylpenicillin, IM, 2.4MU | Amended |
| Doxycyline, 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 |
| **12.12 Pubic lice (Pediculosis of the eyelashes or eyebrows** | Yellow petroleum jelly | Added |
| White petroleum jelly | 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 |

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| **GENERAL** |

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:

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| |  |  |  | | --- | --- | --- | | **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 | | *Lymphogranuloma venereum* | Bubo | azithromycin | |

**Point of care testing**

Rapid diagnostic testing of STIs was 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 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).

|  |  |  |
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| **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[[1]](#footnote-2).

**Level of Evidence: III Guidelines**

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| **12.1 VAGINAL DISCHARGE SYNDROME (VDS)** |

Age cut-off criterion: *deleted from VDS algorithm*

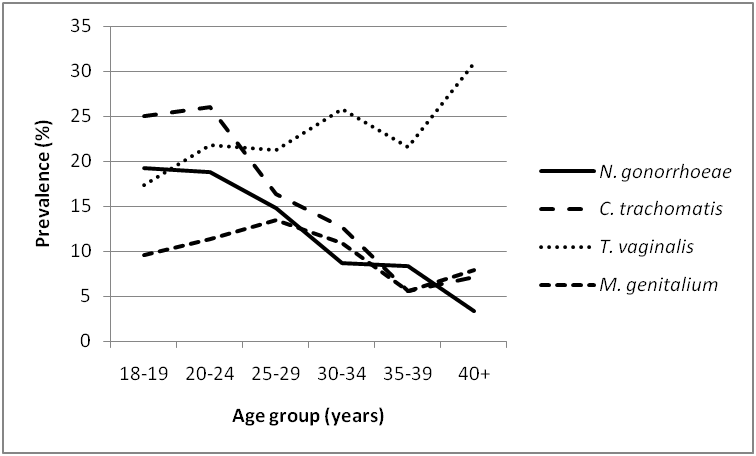
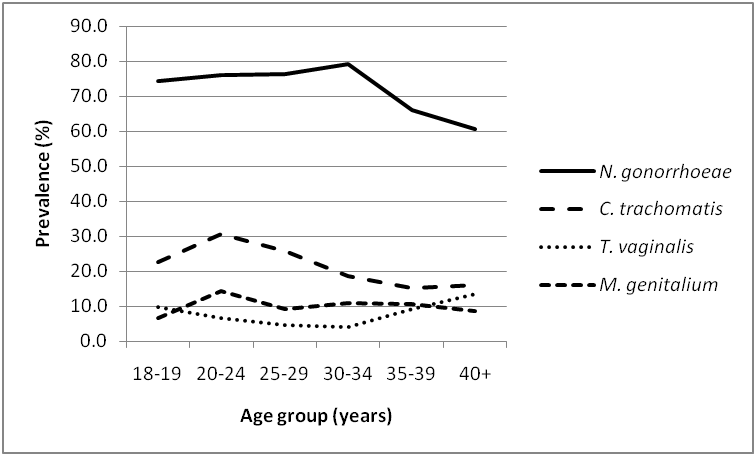
Sexual activity criterion: *added to VDS algorithm*

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.



**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:

Bacterial vaginosis or candidiasis and no STI co-infection: 20%

Bacterial vaginosis or candidiasis and STI co-infection: 14%

STI infection only: 19%

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)[[2]](#footnote-3) 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 |
| 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[[3]](#footnote-4) 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 datain 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 algorithmwomen>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 NAS study (2014-2015)[[4]](#footnote-5), 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[[5]](#footnote-6) 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:**

1. Age be removed as a criterion for treating chlamydia and gonococcal infections versus bacterial vaginosis.
2. Sexual activity be added as a criterion for syndromic treatment of STI when presenting with VDS.
3. The VDS algorithm(s) differentiate clinically between candidiasis and bacterial vaginosis.
4. 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,mayguide 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*

The PHC Committee considered that 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 were raised as 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**

**REFERRAL**

**Recommendation:** Patients failing treatment as indicated in the VDS algorithm must be referred. Their management should be included in the Adult Hospital Level STG.

*Rationale:* Specimens must be sent for specific antibiotic susceptibility tests, if there is treatment failure at primary level of care.

**Level of Evidence: III Expert opinion**

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| **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 be 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. The PHC Committee was of the opinion that it was 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**

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| **12.5 GENITAL ULCER SYNDROME (GUS)** |

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[[6]](#footnote-7)**

**Aciclovir-resistant ulcers**

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

Although, *Haemophilus ducreyi*is uncommon[[7]](#footnote-8), 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**

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| **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[[8]](#footnote-9).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 InfectiousDiseases Society of America Guidelines: *Lymphogranuloma venereum* 2015: Clinical Presentation, Diagnosis, and Treatment.[[9]](#footnote-10)

**Level of Evidence: III Surveillance study, Guidelines**

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| **12.7 BALANITIS/BALANOPOSTHITIS (BAL)** |

Benzathine benzylpenicillin, IM, 2.4MU:*deleted*

*Syphilitic balanitis* is very rare[[10]](#footnote-11)[[11]](#footnote-12)[[12]](#footnote-13) 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[[13]](#footnote-14)**

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| **12.12 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**

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| **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[[14]](#footnote-15)**

**Note:** NEMLC Committee member has recently forwarded an article for consideration of amoxicillin+probenecid for syphilis; the PHC Committee will review the evidence, accordingly.

**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[[15]](#footnote-16)**

**Budget impact analysis:** It is anticipated that the budget impact would be less for the syndromic management of STIs when guided by the updated algorithms compared to the current PHC 2014 STI algorithms. An estimated budget impact will be costed for tabling with the final STI chapter (using direct medicine costs only).

1. Centers for Disease Control and Prevention. 2015 Sexually Transmitted Diseases Treatment Guidelines. <https://www.cdc.gov/std/tg2015/> [↑](#footnote-ref-2)
2. 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. [↑](#footnote-ref-3)
3. 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. [↑](#footnote-ref-4)
4. 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. [↑](#footnote-ref-5)
5. NDoH: Comprehensive STI Clinical Management Guidelines, draft version. [↑](#footnote-ref-6)
6. 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> [↑](#footnote-ref-7)
7. 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)* [↑](#footnote-ref-8)
8. 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. [↑](#footnote-ref-9)
9. Stoner BP, Cohen SE. Lymphogranuloma Venereum 2015: Clinical Presentation, Diagnosis, and Treatment. Clin Infect Dis. 2015 Dec 15;61Suppl 8:S865-73. [↑](#footnote-ref-10)
10. - Abdennader S, Janier M, Morel P. Syphilitic balanitis of Follmann: three case reports. Acta DermVenereol. 2011 Mar;91(2):191-2. [↑](#footnote-ref-11)
11. 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. [↑](#footnote-ref-12)
12. 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. [↑](#footnote-ref-13)
13. 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. [↑](#footnote-ref-14)
14. 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> [↑](#footnote-ref-15)
15. 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> [↑](#footnote-ref-16)