STI Treatment Guidelines

Teodora Wi

Training Course in Sexual and Reproductive Health Research 2017

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STI treatment guidelines

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- Genital herpes simplex
- *Treponema pallidum* (syphilis)
- Syphilis screen and treat for pregnant women

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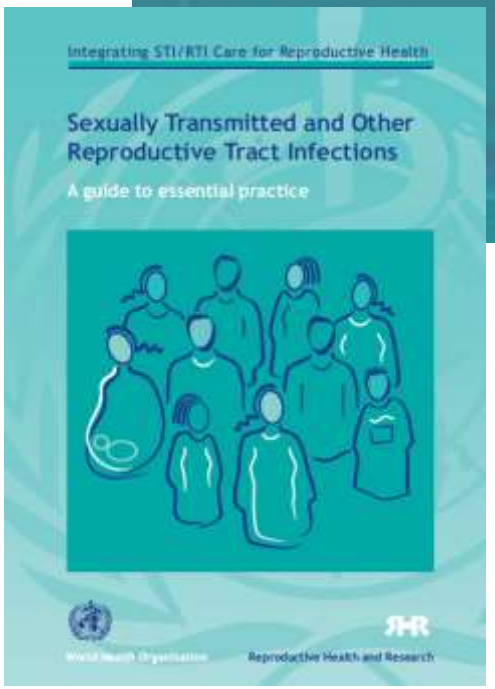
Rationale

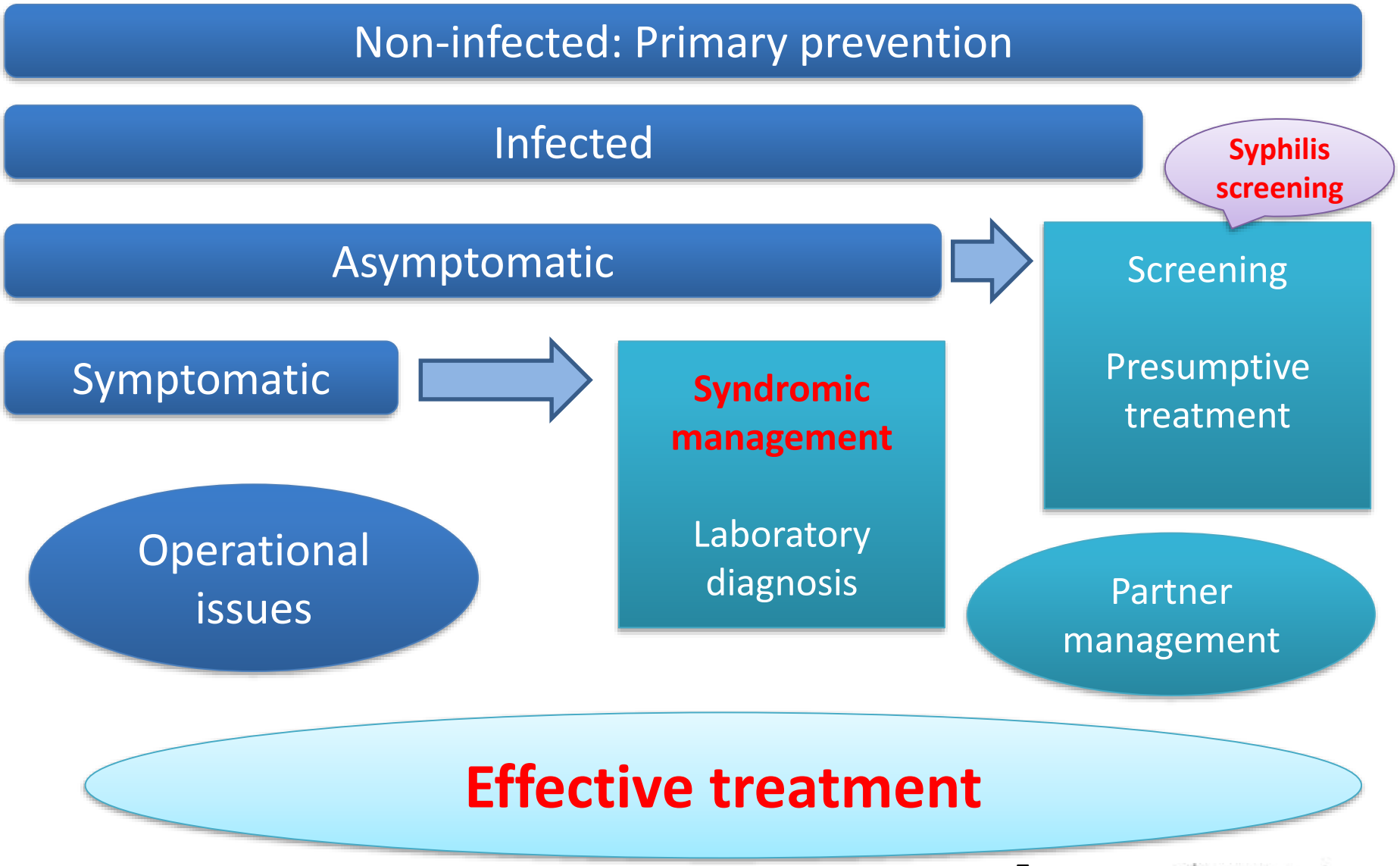
- STI guidelines last updated in 2003
- Concerns about STI syndromic case management
- Treatment issues related to antimicrobial resistance in *N. gonorrhoeae*
- Scaling up syphilis screening – increasing availability of rapid syphilis test, testing flowcharts



STI guidelines: Prevention, Management and Control

Phases	Topics	Timeframe
Phase 1	**Treatment of specific STIs:** Chlamydia trachomatis (chlamydia), Neisseria gonorrhoeae (gonorrhoea), HSV-2 (genital herpes) and Treponema pallidum (syphilis) **Syphilis screening and treatment of pregnant women** **STI syndromic approach** **Clinical management package**	November 2013 – December 2016 May 2016 – December 2017
Phase 2	**STI prevention:** condoms, behaviour change communication, biomedical interventions and vaccines	2017–2018
Phase 3	**Treatment of specific STIs and reproductive tract infections** (RTIs) not addressed in Phase 1: Trichomonas vaginalis (trichomoniasis), bacterial vaginosis, Candida albicans (candidiasis), Hemophilus ducreyi (chancroid), Klebsiella granulomatis (donovanosis), human papillomavirus (HPV; genital warts/cervical cancer), Sarcoptes scabiei (scabies) and Phthirus pubis (pubic lice)	2017–2018
Phase 4	**STI laboratory diagnosis and screening**	2017–2018

WHO STI Guidelines



Objective of the guidelines

- Provide evidence-based guidance on treatment of specific STI *N. gonorrhoeae, Chlamydia trachomatis and Treponema pallidum* and syphilis screening and treatment for pregnant women
- Support countries to update their national guidelines

Target audience

- Health-care providers at all levels (primary, secondary and tertiary) of the health-care system
- Individuals working in sexual and reproductive health programmes, such as HIV/AIDS, family planning, maternal and child health and adolescent health
- Policy-makers, managers, programme officers and other professionals implementing STI management interventions at regional, national and subnational levels.

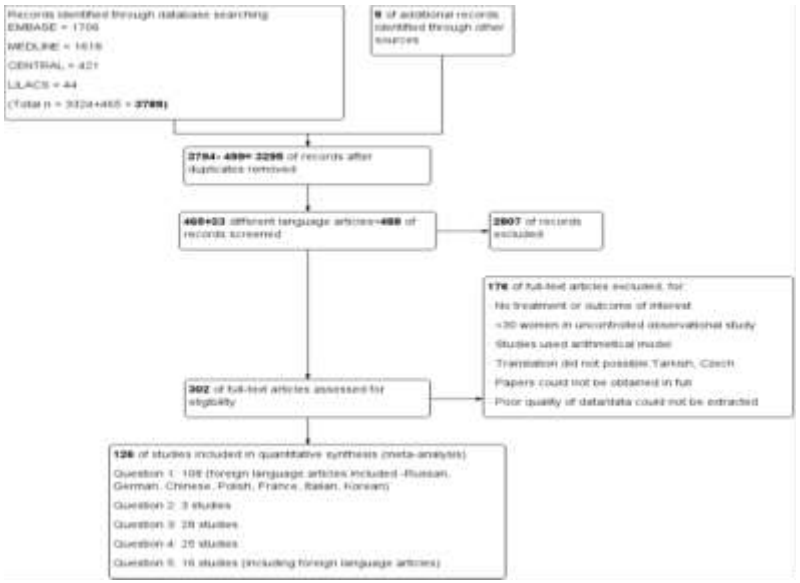
Guideline Development Group

- WHO Steering Committee – from different WHO departments and representation from regions
  - Inventory of existing guidelines
  - Determine the need for an updated guideline
  - Draft initial PICO
- STI guideline development group – 33 STI experts with different expertise
  - 4 subgroups to focus on specific STIs
  - Finalize the scoping document – PICO methods
  - Involve in the entire process of guideline development
- STI external development group – 15-18 STI experts
  - Reviewed the final document

Review of evidence

- PICO question and components - benefits, harms, patient values, acceptability, feasibility, equity and costs
- Search terms and search strategies developed
- Pre-existing evidence
  - Previously published guidelines that included systematic reviews of the literature
  - Existing systematic reviews
    - Cochrane Library suite of databases (Cochrane Database of Systematic Reviews [CDSR], Database of Abstracts of Reviews of Effects [DARE], Health Technology Assessment [HTA] database and the American College of Physicians [ACP] Journal Club)
- New systematic review of randomized controlled trials (RCTs) and non-randomized studies

Population	Intervention	Comparator	Outcome
Adults and adolescents, HIV-positive patients, MSM with uncomplicated genital (cervix, urethra) and anorectal gonococcal infections	Ceftriaxone ≥ 250 mg IM × 1	Single therapy: Azithromycin 1–2 g po × 1 Cefixime 400 mg po × 1 Cefixime 800 mg po × 1 Cefixime 400 mg po × 2 Gentamicin 240 mg IM × 1 Spectinomycin 2 g IM × 1 Kanamycin 2 g IM × 1 Quinolones (just in vitro resistance data) Ceftriaxone 125 mg IM × 1 Dual therapy versus single therapy: And multiple combinations of Cefixime + doxycycline (or azithromycin) versus cefixime alone And multiple combinations of Ceftriaxone + doxycycline (or azithromycin) versus ceftriaxone alone	Critical: Microbiological cure, STI complications, clinical cure, transmission to partners, compliance, N. gonorrhoeae antimicrobial in vitro resistance, side-effects (including allergy, toxicity) Important: HIV transmission and acquisition, quality of life



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GRADE

- Evidence Profile
- Evidence to decision framework
- Making recommendations
  - STI GDG group
  - Follow-up teleconferences

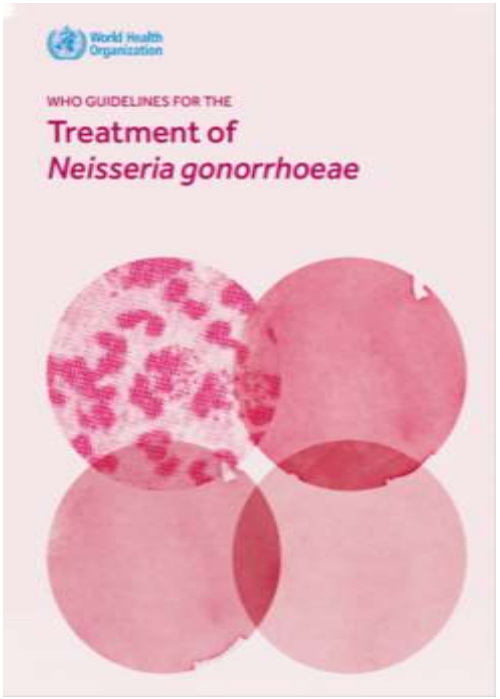
	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST-EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

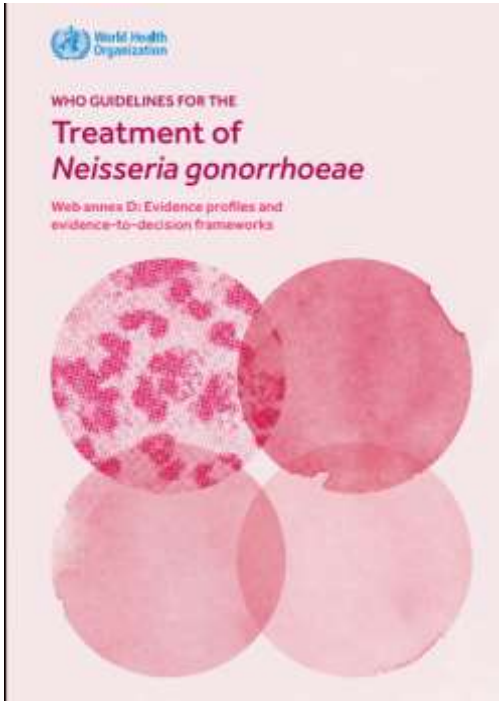
Assessment of quality/certainty of the evidence at four levels

- **High** – We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate** – We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low** – Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- **Very low** – We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Implication of strong and conditional recommendations using the GRADE approach

Implications	Strong recommendation "The WHO STI guideline recommends… "	Conditional recommendation "The WHO STI guideline suggests… "
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.





http://www.who.int/reproductivehealth/publications/rtis/gonorrhoea-treatment-guidelines/en/

NEISSERIA GONORRHOEA

Key Messages : *N. gonorrhoea*

- Local resistance data to determine the choice of therapy (both for dual therapy and single therapy).
- Use of dual therapy over single therapy
  - Ceftriaxone 250 mg or Cefixime 400 mg plus Azithromycin 1 gram
- Quinolones are no longer recommended
- Oropharyngeal infection
- Treatment Failure: increase dose
  - Ceftriaxone 500 mg plus Azithromycin 2 grams
  - Gentamicin or Spectinomycin plus Azithromycin 2 grams
- For all neonates, topical ocular prophylaxis for the prevention of gonococcal and chlamydial ophthalmia neonatorum.

Genital and anorectal gonococcal infections

The WHO STI guideline recommends that local resistance data should determine the choice of therapy (both for dual therapy and single therapy).

Good practice statement

In settings where local resistance data are not available, the WHO STI guideline suggests dual therapy over single therapy for people with genital or anorectal gonorrhoea.

- *Dual therapy* (one of the following)
  - ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose
  - cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose
- *Single therapy* (one of the following, based on recent local resistance data confirming susceptibility to the antimicrobial)
  - ceftriaxone 250 mg IM as a single dose
  - cefixime 400 mg orally as a single dose
  - spectinomycin 2 g IM as a single dose.

Conditional recommendation, very low quality evidence

Oropharyngeal gonococcal infections

In adults and adolescents with gonococcal oropharyngeal infections, the WHO STI guideline suggests dual therapy over single therapy.

- *Dual therapy* (one of the following)
  - ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose
  - cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose

- *Single therapy* (based on recent local resistance data confirming susceptibility to the antimicrobial)
  - ceftriaxone 250 mg IM as single dose.

Conditional recommendation, low quality evidence

Retreatment of gonococcal infections after treatment failure

In people with gonococcal infections who have failed treatment, the WHO STI guideline suggests the following options.

- If reinfection is suspected, re-treat with a WHO-recommended regimen, reinforce sexual abstinence or condom use, and provide partner treatment.
- If treatment failure occurred after treatment with a regimen not recommended by WHO, re-treat with a WHO-recommended regimen.
- If treatment failure occurred and resistance data are available, re-treat according to susceptibility.
- If treatment failure occurred after treatment with a WHO-recommended single therapy, re-treat with WHO-recommended dual therapy.
- If treatment failure occurred after a WHO-recommended dual therapy, re-treat with one of the following dual therapies:

Conditional recommendation, very low quality evidence

Retreatment of gonococcal infections after treatment failure (dual therapy options)

- ceftriaxone 500 mg IM as a single dose PLUS azithromycin 2 g orally as a single dose
- cefixime 800 mg orally as a single dose PLUS azithromycin 2 g orally as a single dose
- gentamicin 240 mg IM as a single dose PLUS azithromycin 2 g orally as a single dose
- spectinomycin 2 g IM as a single dose (if not an oropharyngeal infection) PLUS azithromycin 2 g orally as a single dose.

Conditional recommendation, very low quality evidence

Gonococcal ophthalmia neonatorum

In neonates with gonococcal conjunctivitis, the WHO STI guideline suggests one of the following treatment options:

- ceftriaxone 50 mg/kg (maximum 150 mg) IM as a single dose
- kanamycin 25 mg/kg (maximum 75 mg) IM as a single dose
- spectinomycin 25 mg/kg (maximum 75 mg) IM as a single dose.

Conditional recommendation, very low quality evidence

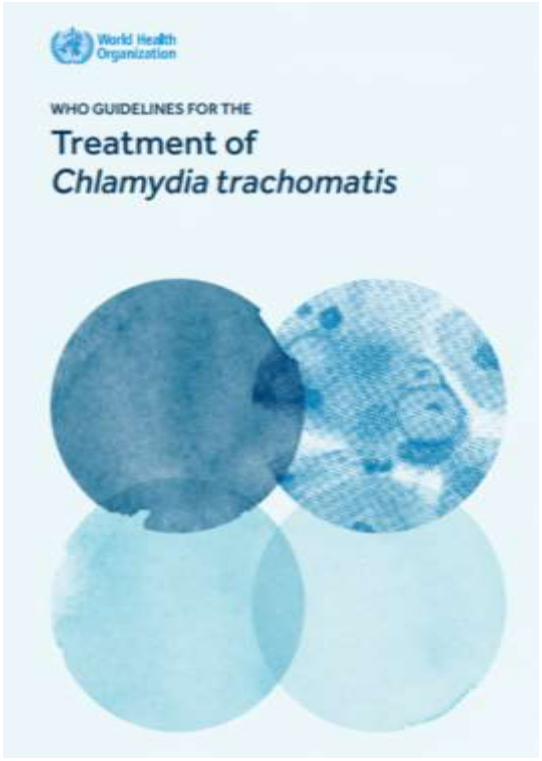
Prevention of gonococcal and chlamydial ophthalmia neonatorum.

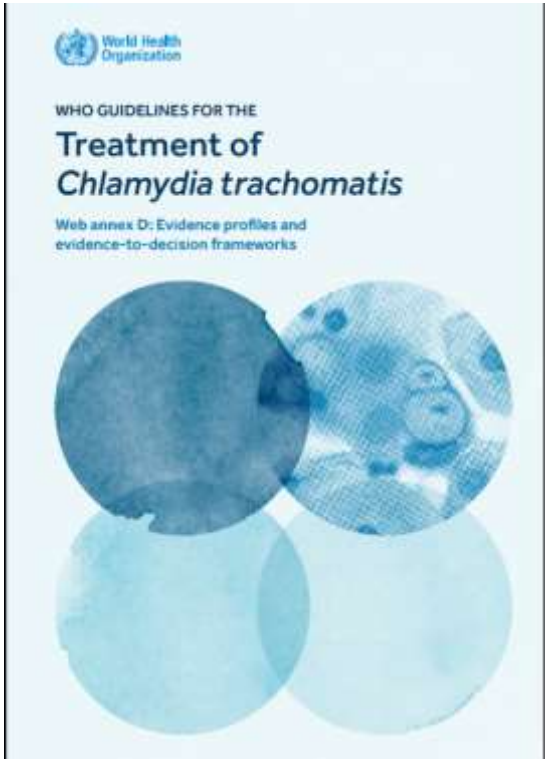
- For all neonates, the WHO STI guideline recommends topical ocular prophylaxis for the prevention of gonococcal and chlamydial ophthalmia neonatorum.

Strong recommendation, low quality evidence

- For ocular prophylaxis, the WHO STI guideline suggests one of the following options for topical application to both eyes immediately after birth:
  - tetracycline hydrochloride 1% eye ointment
  - erythromycin 0.5% eye ointment
  - povidone iodine 2.5% solution (water-based)
  - silver nitrate 1% solution
  - chloramphenicol 1% eye ointment.

Conditional recommendation, low quality evidence





http://www.who.int/reproductivehealth/publications/rtis/chlamydia-treatment-guidelines/en/

Chlamydia trachomatis

Key Messages : C. trachomatis and LGV

- C. trachomatis
  - Azithromycin or Doxycline remain to be treatment of choice
  - Ano-rectal infection: Doxycline over Azithromycin
- Lymphogranuloma venereum
  - doxycycline 100 mg orally twice daily for 21 days over azithromycin 1 g orally, weekly for 21 days

Uncomplicated genital infection

The WHO STI guideline suggests treatment with one of the following options:

- azithromycin 1 g orally as a single dose
- doxycycline 100 mg orally twice a day for 7 days

or one of these alternatives:

- tetracycline 500 mg orally four times a day for 7 days
- erythromycin 500 mg orally twice a day for 7 days
- ofloxacin 200–400 mg orally twice a day for 7 days.

Conditional recommendation, moderate quality evidence

Ano-rectal infection

The WHO STI guideline suggests treatment with doxycycline 100 mg orally twice a day for 7 days over azithromycin 1 g orally as a single dose.

Conditional recommendation, low quality evidence

Genital infection in pregnant women

- Azithromycin over erythromycin

  Strong recommendation, moderate quality evidence

- Azithromycin over amoxicillin.
- Amoxicillin over erythromycin.

  Conditional recommendation, low quality evidence

- Dosages:
  - azithromycin 1 g orally as a single dose
  - amoxicillin 500 mg orally three times a day for 7 days
  - erythromycin 500 mg orally twice a day for 7 days.

Lymphogranuloma venereum

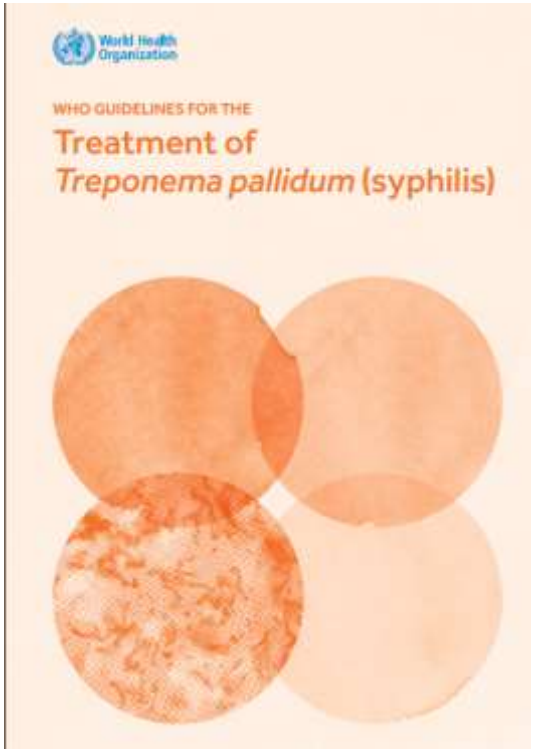
The WHO STI guideline suggests treatment with doxycycline 100 mg orally twice daily for 21 days over azithromycin 1 g orally, weekly for 3 weeks.

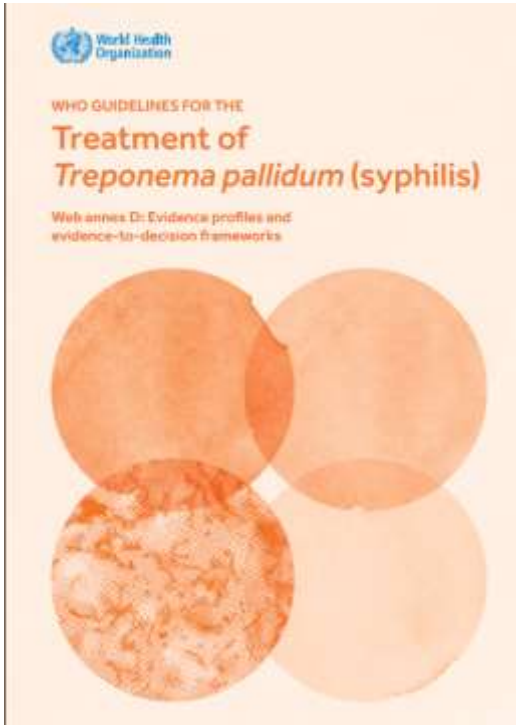
Conditional recommendation, very low quality evidence

Neonatal conjunctivitis

- Azithromycin 20 mg/kg/day orally, one dose daily for 3 days, over erythromycin 50 mg/kg/day orally, in four divided doses daily for 14 days.

Strong recommendation, very low quality evidence





http://www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/

Treponema pallidum (syphilis)

Key Message: Early syphilis (primary, secondary, early latent < 2 years)

	Adults and Adolescents	Pregnant Women
Drug of Choice	Benzathine penicillin G 2.4 million units IM QD x 1	Benzathine penicillin G 2.4 million units IM QD x 1
Alternative	Procaine penicillin G 1.2 million units IM QD x 10-14 days	Procaine penicillin G 1.2 million units IM QD x 10-14 days
Penicillin allergy or stock out	Doxycycline 100 mg BID x 14 days or Ceftriaxone 1 g IM, QD x 10-14 days or in special circumstances Azithromycin 2 g QD x 1	Erythromycin 500 mg QID x 14 days* or Ceftriaxone 1 g IM, QD x 10-14 days* or in special circumstances Azithromycin 2 g QD x 1* *with caution

Early syphilis (primary, secondary, early latent < 2 years) in adults and adolescents

- Benzathine penicillin G 2.4 million units once intramuscularly over no treatment.

Strong recommendation, very low quality evidence

- Benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin G 1.2 million units 10-14 days intramuscularly
- When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy) or are not available (e.g. due to stock outs), the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 14 days or ceftriaxone 1 g intramuscularly once daily for 10-14 days or in special circumstances azithromycin 2 g once orally.

Conditional recommendation, very low quality evidence

Early syphilis (primary, secondary, early latent < 2 years) in pregnant women

- Benzathine penicillin G 2.4 million units once intramuscularly over no treatment.

Strong recommendation, very low quality evidence

- Benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin 1.2 million units intramuscularly once a day for 10 days.

- When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock outs), the WHO STI guideline suggests using, with caution, erythromycin 500 mg orally four times daily for 14 days or ceftriaxone 1 g intramuscularly once daily for 10-14 days or azithromycin 2 g once orally.

Conditional recommendation, very low quality evidence

Key Message: LATE SYPHILIS (infection of more than two years' duration without evidence of treponemal infection)

	Adults and Adolescents	Pregnant Women
Drug of Choice	Benzathine penicillin G 2.4 million units IM QD x 3 consecutive weeks	Benzathine penicillin G 2.4 million units IM QD 3 consecutive weeks
Alternative	Procaine penicillin G 1.2 million units IM QD x 10-20 days	Procaine penicillin G 1.2 million units IM QD x 20 days
Penicillin allergy or stock out	Doxycycline 100 mg BID x 30 days	Erythromycin 500 mg QID x 30 days (with caution)

Because syphilis during pregnancy can lead to severe adverse complications to the fetus or newborn, **stock-outs of benzathine penicillin for use in antenatal care should be avoided**.

LATE SYPHILIS (infection of more than two years' duration without evidence of treponemal infection) Adults and adolescents

- Benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment

Strong recommendation, very low quality evidence

- Benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units once a day for 20 days
- When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (due to stock outs), the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 30 days.

Conditional recommendation, very low quality evidence

LATE SYPHILIS (infection of more than two years' duration without evidence of treponemal infection) Pregnant women

- Benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment

Strong recommendation, very low quality evidence

- Benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units once a day for 20 days
- When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (due to stock outs), the WHO STI guideline suggests with caution using erythromycin 500 mg orally four times daily for 30 days.

Conditional recommendation, very low quality evidence

Key Message: Congenital syphilis

- In infants with confirmed congenital syphilis or infants who are clinically normal, but mother with syphilis was not treated, inadequately treated (including treated within 30 days of delivery) or treated with non-penicillin regimen:
  - Aqueous benzyl penicillin 100,000-150,000 U/kg/day intravenously for 10-15 days
  - Procaine penicillin 50,000 U/kg/day single dose intramuscularly for 10-15 days
- In infants who are clinically normal and the mother had syphilis and was adequately treated with no signs of re-infection:
  - closely monitor the infants over treatment
  - Benzathine penicillin G 50,000 U/kg/day single dose intramuscularly

Infants

In infants with confirmed congenital syphilis or infants who are clinically normal, but mother with syphilis was not treated, inadequately treated (including treated within 30 days of delivery) or treated with non-penicillin regimen, the WHO STI guideline suggests aqueous benzyl penicillin or procaine penicillin.

Dosages:

- Aqueous benzyl penicillin 100,000-150,000 U/kg/day intravenously for 10-15 days
- Procaine penicillin 50,000 U/kg/day single dose intramuscularly for 10-15 days

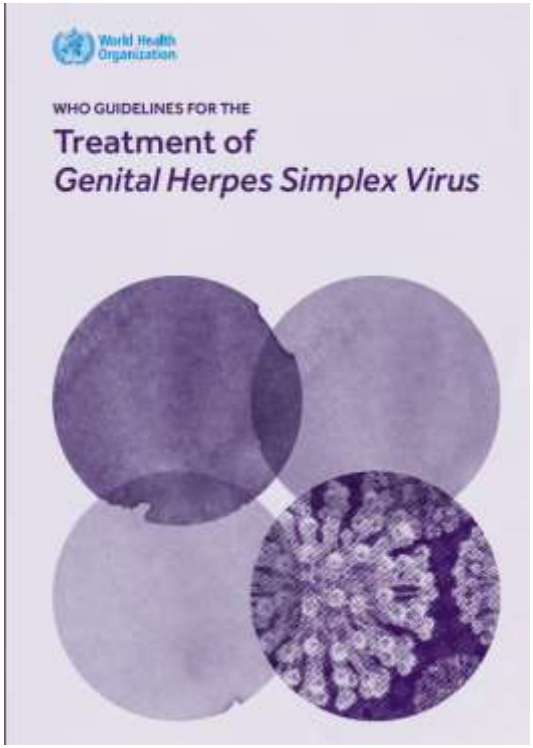
Conditional recommendation, very low quality evidence

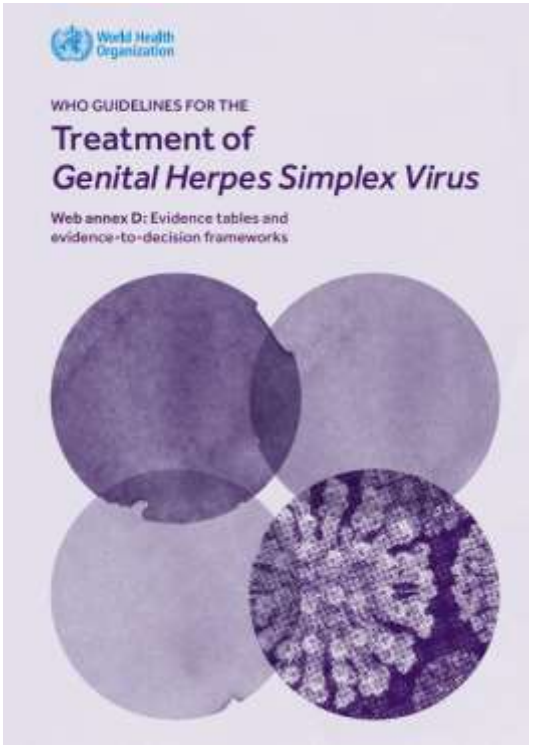
Infants

- In infants who are clinically normal and the mother had syphilis and was adequately treated with no signs of re-infection, the WHO STI guideline suggests to closely monitor the infants over treatment.

Conditional recommendation, very low quality evidence

- Treatment: benzathine penicillin G 50,000 U/kg/day single dose intramuscularly





http://www.who.int/reproductivehealth/publications/rtis/genital-HSV-treatment-guidelines/en/

Genital herpes simplex virus

Key Messages: Genital Herpes Simplex Virus

Primary	Episodic	Suppressive
Acyclovir 400 mg TID x 10 days Acyclovir 200 mg 5 x day x 10 days Valacyclovir 500 mg BID x 10 days Famciclovir 250 mg TID x 7-10 days	Acyclovir 400 mg TID x 5 days Acyclovir 800 mg BID x 3 day Acyclovir 800 mg TID x 2 days Valacyclovir 500 mg BID x 3 days Famciclovir 250 mg TID x 5 days	Acyclovir 400 mg BID Valacyclovir 500 mg OD Famciclovir 250 mg BID

Suppressive therapy: Individuals who have frequent recurrences (such as four to six times per year or more), severe symptoms or episodes which cause distress will likely choose suppressive therapy over episodic therapy.
PLHIV: increase dosages for episodic and suppressive therapy

Key Messages: Genital Herpes Simplex Virus HIV positive and immunocompromise

Primary	Episodic	Suppressive
Acyclovir 400 mg TID x 10 days Acyclovir 200 mg 5 x day x 10 days Valacyclovir 500 mg BID x 10 days Famciclovir 250 mg TID x 10 days	Acyclovir 400 mg TID x 5 days Valacyclovir 500 mg BID x 5 days Famciclovir 250 mg TID x 5 days	Acyclovir 400 mg BID Valacyclovir 500 mg BID Famciclovir 500 mg BID

Suppressive therapy: Individuals who have frequent recurrences (such as four to six times per year or more), severe symptoms or episodes which cause distress will likely choose suppressive therapy over episodic therapy.
PLHIV: increase dosages for episodic and suppressive therapy

First clinical episode of genital HSV infection

- Treatment over no treatment.

Strong recommendation, moderate quality evidence

- Standard dose of acyclovir over valacyclovir or famciclovir.

Dosages:

- Acyclovir 400 mg orally 3 times a day for 10 days (standard dose)
- Acyclovir 200 mg orally 5 times a day for 10 days
- Valacyclovir 500 mg orally twice a day for 10 days
- Famciclovir 250 mg orally 3 times a day for 10 days

Conditional recommendation, moderate quality evidence

Recurrent clinical episode of genital HSV infection (episodic therapy)

- Treatment over no treatment
- Acyclovir over valacyclovir or famciclovir.

Dosages:

- Acyclovir 400mg orally three times a day for 5 days, 800mg twice a day for 5 days, or 800mg three times a day for 2 days
- Valacyclovir 500 mg orally twice a day for 3 days
- Famciclovir 250 mg orally twice a day for 5 days

Conditional recommendation, moderate quality evidence

Recurrent clinical episode of genital HSV infection (episodic therapy)

Dosages for people living with HIV and people who are immunocompromised

- Acyclovir 400mg orally three times a day for 5 days
- Valacyclovir 500 mg orally twice a day for 5 days
- Famciclovir 250 mg orally twice a day for 5 days

Conditional recommendation, moderate quality evidence

Recurrent clinical episodes of genital HSV infections that are frequent, severe or cause distress (suppressive therapy)

- Suppressive therapy over episodic therapy

Conditional recommendation, moderate quality evidence

- Acyclovir over valacyclovir or famciclovir for suppressive therapy.

Dosages:

- Acyclovir 400mg orally twice a day
- Valacyclovir 500mg orally once a day
- Famciclovir 250 mg orally twice a day

Conditional recommendation, low quality evidence

Recurrent clinical episodes of genital HSV infections that are frequent, severe or cause distress (suppressive therapy)

Dosages for people living with HIV and people who are immunocompromised

- Acyclovir 400mg orally twice a day
- Valacyclovir 500mg orally twice a day
- Famciclovir 500 mg orally twice a day

Conditional recommendation, low quality evidence