



A service within The Alfred,
a member of Bayside Health

CPG C5

CLINICAL MANAGEMENT OF UNCOMPLICATED SYPHILIS INFECTION (EARLY AND EARLY LATENT)

GUIDELINE STATUS: FINAL 19/05/2008

REVIEW DATE: 19/05/2009

AUTHOR: MR BUSH, DM LEE

SCOPE OF PRACTICE

TARGET POPULATION

- Clients with a presumptive clinical diagnosis of uncomplicated syphilis from clinical presentation, history, and or on clinical examination.
- Clients with confirmed uncomplicated syphilis through PCR testing
- Clients with serologically confirmed late latent (>24 months) syphilis with no evidence of neurological or cardiovascular involvement
- Clients who present as a contact of laboratory confirmed syphilis infection

EXCLUSION CRITERIA

- Clients with tertiary or neurological and or cardiovascular complications
- Clients who are pregnant or breast feeding
- Clients with ongoing symptoms post treatment
- Clients who are HIV positive

GUIDELINE OBJECTIVES AND ANTICIPATED OUTCOMES

- Provide treatment for clients with a confirmed diagnosed infection or presumptive treatment for symptomatic clients
- Prevent long-term complications resulting from early syphilis infection
- Identification of individual STI risk and provision of appropriate STI screening
- Identify public health risks to control infections by:
 - Provision of STI education and information
 - Identification and exploration of sexual risk taking behaviours
 - Partner notification and treatment
 - Test of reinfection/test of cure where appropriate
 - Monitoring antimicrobial resistance

BACKGROUND

CONDITION DESCRIPTION

The causative organism of syphilis is a spirochaete, *Treponema pallidum*.^{1,2,3} Syphilis as a disease can be classified into three stages – primary (1^o), secondary (2^o) and tertiary (3^o). The infectious period of untreated syphilis is the first 12 months and possibly up to 24 months of acquiring the infection. There is a latent period where the individual is non infectious, which may persist for decades.^{1,2,3} Humoral immunity to syphilis is partially protective and reinfections occur.^{1,2,3} Syphilis is a treatable infection and fully curable with adequate therapy if provided before advanced disease develops.^{1,2,3} The presence of *T. pallidum* as muco-cutaneous lesions in the urethra, rectum and the vaginal may facilitate the acquisition and transmission of HIV.^{1,2,3}

SYPHILIS CLASSIFICATION	
STAGE	DESCRIPTION
PRIMARY	Chancre, regional lymphadenopathy
SECONDARY	Varied dermatologic lesions
LATENT- asymptomatic	Early latent syphilis (infection <2 yr duration), infectious lesions may recur Late latent syphilis (infection > 2 yr duration), recurrences are rare
LATE OR TERTIARY- symptomatic	Includes benign tertiary syphilis, cardiovascular syphilis, and neurosyphilis (asymptomatic neurosyphilis, meningovascular neurosyphilis)

Table C5.1: Classification of syphilis

PRIMARY SYPHILIS	CLINICAL FEATURES
<ul style="list-style-type: none"> • Incubation Period – Mean 21 days (10 – 90 days). Chancre or primary lesion at site of inoculation • Usually single, smooth, dull flat surface with edge • Indurated as a soft tissue that becomes extremely firm • Painless, non tender • Lesions in men may be found on any part of the external genitalia including prepuce, glans, shaft, coronal sulcus, and on lips, buccal cavity, tongue, tonsil and pharynx • Oral and rectal chancres may remain undetected • Lesions in women may be on the labium majus, labium minus, fourchette, clitoris or cervix 	
SECONDARY SYPHILIS	CLINICAL FEATURES
<ul style="list-style-type: none"> • Signs appear 7-10 weeks post exposure or 6-8 weeks after chancre appears • Time after exposure: 6 weeks to 6 months • Mild fever, lethargy, headaches • Swollen lymph nodes • Non itchy skin rash, macular papular palms and soles, face, scalp, external genitalia 	

Table C5.2: Clinical features of syphilis ^{2,3,4} (photos courtesy of MSHC)

EPIDEMIOLOGY

Syphilis is transmitted sexually, parenterally, congenitally and occupational exposures have also been reported. ^{1,2,3} Since widespread use of penicillin, the incidence of tertiary syphilis and generally infection with syphilis has declined. More recently there has been a marked rise of syphilis, diagnosed mostly in homosexually active men in almost all cities across the world. ⁴ In Victoria, notifications of syphilis have also risen significantly and between 2000 and 2006, the annual infectious syphilis notifications rose from 9 to 234 cases. ⁴ A significant proportion of these infections have occurred in HIV positive MSM and some of the transmission is thought to occur through oral sex. ^{1,2,3}

SEQUELAE- SYPHILIS DISEASE MANIFESTATIONS ^{2,3}

- Gummatous syphilis
- Cardiovascular syphilis
- Neurosyphilis
- Congenital syphilis

INVESTIGATIONS AND DIAGNOSIS

Syphilis is detected through a variety of means

- Microscopy- Darkfield examination or Dark Ground Inspection (DGI)
- Polymerase chain reaction (PCR)
- Serology

MICROSCOPY

Clients with a genital ulcerative lesion and who are determined as epidemiologically at risk of syphilis should have a DGI performed. Clients presenting with a rash consistent with secondary syphilis where an exudate may be obtained from the rash can also be tested for DGI or PCR. DGI sensitivity is up to 80% in experienced laboratories. ⁵

COLLECTION OF MICROBIOLOGICAL SPECIMENS FOR DGI ^{1,5}

- Universal precautions
- Clean suspected lesion with saline
- Serous fluid may be elicited by gently squeezing
- Avoid causing bleeding
- Collect fluid on edge of a cover slip – transfer to a slide
- place a drop of saline on the slide if insufficient fluid obtained, then apply cover slip
- Take slide to lab immediately for DGI
- DGI of suspected oral lesions should not be attempted because of the presence of non-pathogenic oral treponemes.

Table C5.3: DGI guidelines

POLYMERASE CHAIN REACTION (PCR)

PCR *Treponema pallidum* may be collected from ano-genital lesions. ⁵ The same swab used for collection of specimen for DGI may also be then placed in a plain collection tube for a PCR *T. pallidum* through VIDRL.

SEROLOGICAL SPECIMEN

All patients presenting with a genital ulcerative lesion should be tested for syphilis serologically. Serological testing for syphilis consists of Non-specific (Non-treponemal) tests and Specific (Treponemal) tests. ^{1,2,3,5} At risk core groups should be serologically screened for syphilis as routine.

SYPHILIS SEROLOGY

Primary Screen on untested serum	RPR EIA
Confirmatory testing on any positive result	RPR TPPA EIA
Recent primary infection	IgM EIA (remains positive up to 6 months so can include asymptomatic infection and primary or secondary syphilis)
Discordant result (between TPPA and an EIA)	FTA-abs – more specific than EIA IgM

Table C5.4: Syphilis serology

NON SPECIFIC SCREENING TEST: RPR- RAPID PLASMA REAGIN ⁵

- Performed as a routine screening test for syphilis
- Test useful for patients treated for syphilis as the titre dilution reduces after treatment and used as a guide for effectiveness of treatment. The RPR will become non reactive by about 12 months in 1° syphilis and 18-24 months for 2° syphilis and early latent disease
- A positive RPR 12 month after treatment for 1° syphilis or 2 years for 2° syphilis may indicate inadequate treatment, persistent infection or reinfection
- Tests becomes reactive 3-4 weeks after infection in up to 75% of 1° syphilis; 100% 2° syphilis (titre usually higher than 1:16) and in about 70% in late disease
- Biological false positive (BFP) can result from viral infections, atypical pneumonia and vaccinations and usually resolves on retesting

SPECIFIC CONFIRMATORY TEST: EIA- RECOMBINANT TREPONEMA PALLIDUM TOTAL ANTIBODY EIA ⁵

- Test remains positive for life following infection
- Sensitivity consensus TPPA/FTA 100%
- Specificity consensus TPPA/FTA 100%
- False positive factors – Nil known to date
- False negative factors – Nil known to date

TREPONEMA PALLIDUM IGM EIA ⁵

- Antibodies are detectable from 1-4 weeks after chancre has formed; lasts up to 6 months. In HIV +ve clients, delayed IgM response and may occur after treatment
- Sensitivity 86.5% (95% CI 74.2 – 94.4)
- Specificity ~90%

TPPA- TREPONEMA PALLIDUM PARTICLE AGGLUTINATION TEST ⁵

- Sensitivity 1° syphilis 88% ; 2° syphilis 100%; latent 97%
- Specificity 95%

FTA-ABS- FLUORESCENT TREPONEMAL ANTIBODY ABSORPTION TEST ⁵

- Sensitivity 1° syphilis 86% ; 2° syphilis 100%; late 73%
- Specificity 97%

INTERPRETATION OF SEROLOGICAL TESTS

RPR	TPPA	FTA ABS	INTERPRETATION
NON REACTIVE	NON REACTIVE	REACTIVE	Primary syphilis with compatible clinical findings
REACTIVE (dilutions may vary)	REACTIVE	REACTIVE	Infectious syphilis (primary, secondary, early latent) If titre <1:8 Past treated syphilis if titre <1:8
NON REACTIVE	REACTIVE	REACTIVE	usually treated syphilis or, early infection (early primary syphilis) or, late latent syphilis (look for evidence of past syphilis test results)
REACTIVE	NON REACTIVE	NON REACTIVE	Biological false positive

Table C5.5: Interpreting syphilis serology

TREATMENT AND MANAGEMENT

TREATMENT INDICATORS^{6,7}

- Clinical symptoms of 1° syphilis (chancre) or 2° syphilis (rash) and epidemiologically linked to communities impacted by high prevalence of syphilis.
- Laboratory confirmed diagnosis of early, early latent or latent untreated syphilis
- Contact of sexual partners who are confirmed to be syphilis seropositive or by laboratory PCR / DGI and who are epidemiologically linked to communities impacted by high prevalence of syphilis.

TREATMENT OF EARLY SYPHILIS 1° OR 2°

- **Benzathine Penicillin 1.8 gm IMI stat**
- **Lignocaine 1% injection dilution**

Long acting penicillin is the gold standard of treatment for syphilis
Clients allergic to Penicillin require MO review and consider possible penicillin desensitisation.

TREATMENT OF LATE LATENT SYPHILIS OR SYPHILIS OF UNKNOWN DURATION

- **Benzathine Penicillin 1.8 gm IMI weekly for 3 weeks**
- **Lignocaine 1% injection dilution**

JARISCH-HERXHEIMER REACTION (JHR)

Following treatment of syphilis with penicillin, 50-80% of clients will experience JHR complication usually within a day of treatment. The characteristics of JHR include fever and an exacerbation of existing lesions. It is self-limiting and resolves within 24 hrs.

The cause of JHR is not completely understood. Patients undergoing treatment of syphilis should be made aware that reactions may develop within 4 hours post treatment, worsening at 6-8 hrs but resolving within 24 hours. It is important to inform patients that if JHR does not resolve within 24 hours that they need to seek medical attention so as to distinguish between JHR and a hypersensitivity reaction. JHR is not a sign of penicillin allergy.

SYMPTOMS OF JHR

- Fever
- Chills
- Headache
- Nausea
- Generally unwell
- General joint aches
- General muscle aches

Table C5.6: JHR

MANAGEMENT

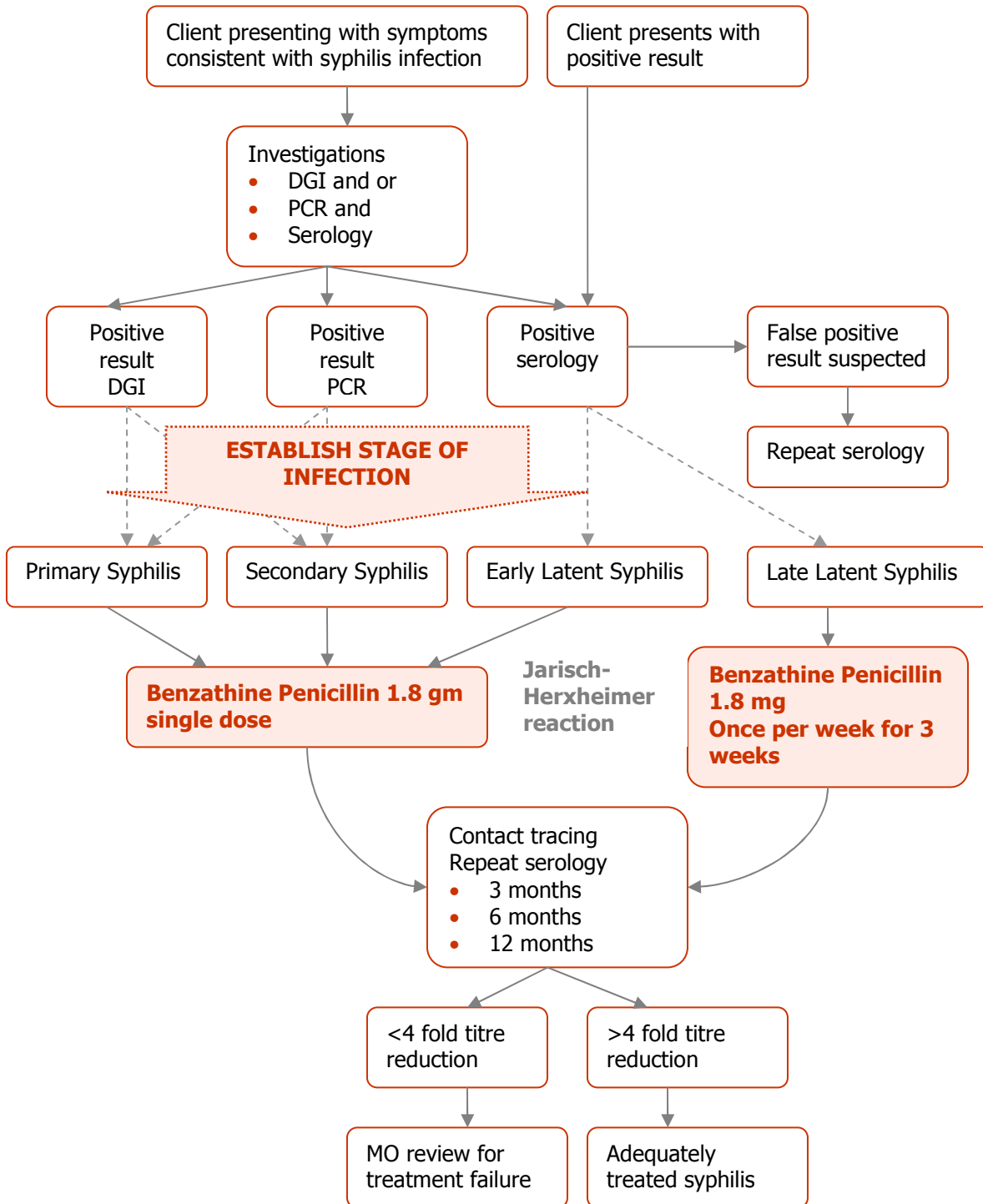
- Review client 7 days post treatment
- The RPR titre is a measure of response to treatment and should decline 4-fold within 6 months post treatment. Patients are advised to return for repeat syphilis serology at -
[Post last treatment]
 - 3 months
 - 6 months
 - 12 months

- Where the RPR remains serofast (no decline in titre) or there is a rise in RPR, refer to a MO for further evaluation and re-treatment. The 6 months serology is really important to see a titre fall in RPR.

PUBLIC HEALTH CONSIDERATIONS - FOLLOW UP AND REVIEW

- Clients with early syphilis (< 24 months) are advised to contact trace all sexual contacts in the past 6 months preceding diagnosis. Contacts include any sexual activity both receptive and insertive involving penile-oral, penile-anal, penile-vaginal sex
- Refraining from sex including oral sex is recommended for a minimum of seven days following treatment and / or until lesion / rash is no longer apparent.
- All clients with positive results will undergo follow up according to MSHC follow up procedures including recall for treatment and results, serological monitoring, test of reinfection, test of cure, Department of Human Services (DHS) notification and surveillance forms, partner notification and assistance in contact tracing.

CLINICAL ALGORITHM



MEDICATION FORMULARY ⁹

DRUG	INDICATIONS	ROUTE	DOSE	FREQUENCY	THERAPEUTIC CLASS/ Poisons Schedule	CONTRAINDICATIONS/ INTERACTIONS	PRECAUTIONS/ ADVERSE EFFECTS
Benzathine Penicillin	Early syphilis – primary, secondary and early latent (<24 months)	IMI	1.8 g	stat	Antibiotic S4 Pregnancy category A	Allergy to penicillins – consider referral for desensitisation	Observe for 20 minutes post injection for anaphylaxis Warn patients about Jarisch-Herxheimer Reaction
						Anaphylaxis Asthma Lactation	Local effects include pain at injection site; atrophy. Hypersensitivity; haematological effects; acute interstitial nephritis
Benzathine Penicillin	Treatment of Late Latent syphilis or syphilis of unknown duration	IMI	1.8 g x 3 doses I week apart	Weekly for 3 weeks	Antibiotic S4 Pregnancy category A	Allergy to penicillins – consider referral for desensitisation	Observe for 20 minutes post injection for anaphylaxis Warn patients about Jarisch-Herxheimer Reaction
						Anaphylaxis Asthma Lactation	Local effects include pain at injection site; atrophy. Hypersensitivity; haematological effects; acute interstitial nephritis
Lignocaine 1%	Anaesthesia at injection site	IMI	1 ml	stat	Local anaesthetic (A)	Known sensitivity or allergy	Pregnancy
						Cimetidine, beta blockers	

REFERENCE

1. Patel R, Wilmot FE. Genital ulcers In: Russell D, Bradford D, and Fairley C, editors. Sexual health medicine. Melbourne: IP Communications; 2005. p. 87-108.
2. Musher DM. Early syphilis. In: Holmes K K, Sparling P F, Mardh P A, Lemon S M, Stamm W E, et al, editors. Sexually transmitted diseases. 3rd ed. New York: McGraw Hill; 1999. p. 479-486.
3. Young H, McMillan A. Syphilis and the endemic treponematoses. In McMillan A, Young H et al. Clinical Practice in Sexually Transmissible Infections. London: Saunders; 2002. p 395-455.
4. Lee DM, Chen MY, Fairley CK. The re-emerge of syphilis among homosexually active men in Melbourne. Australian & New Zealand Journal of Public Health. 2005;29(4): 390-391.
5. Victorian Infectious Disease Reference Laboratory (VIDRL).Introduction to syphilis: Bacterial Serology Manual. Melbourne: VIDRL, Royal Melbourne Hospital. 2006.
6. Melbourne Sexual Health Centre. Treatment guidelines: syphilis. Melbourne: Bayside Health; 2005.
7. Venereology Society of Victoria. National management guidelines for sexually transmissible infections. Melbourne: Venereology Society of Victoria; 2002.
8. ASHM. Australasian Contact Tracing Manual. 3rd ed. Canberra: Department of Health & Ageing. 2006.
9. Therapeutic Guidelines Limited. Therapeutic guidelines antibiotic version 13. Melbourne: Therapeutic Guidelines Limited; 2006.
10. Syphilis. Retrieved May 5th, 2008, from www.cdc.gov/nchstp/dstd/Stats_Trends/1999Surveillance/99pdf/99Section4.pdf.
11. Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. Clinical Microbiology Review. 1995; 8: 1-21.
12. Cummings MC, Lukehart SA, Marra C, Smith BL, Shaffer J, Demeo LR, et al. Comparison of methods for the detection of *Treponema pallidum* in lesions of early syphilis. Sexual Transmitted Disease. 1996; 23:366-9.
13. Tramont EC. *Treponema pallidum* (syphilis). In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and practice of infectious diseases. 5th ed. Philadelphia: Churchill Livingstone, 2000. p.2474-90.
14. Luger AF. Serological diagnosis of syphilis: current methods. In: Young H, McMillan A, eds. Immunological diagnosis of sexually transmitted diseases. New York: Dekker, 1988:250-9.
15. Fischbach FT. Syphilis detection tests. In: A manual of laboratory & diagnostic tests. 6th ed. Philadelphia: Lippincott, 2000:581-83.

16. Sexually transmitted diseases treatment guidelines 2002. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 2008;51(RR-6):18-25,28-30.
17. Romanowski B, Sutherland R, Fick GH, Mooney D, Love EJ. Serologic response to treatment of infectious syphilis. Ann Intern Med 1991;114:1005-9.
18. Syphilis. Retrieved May 19th, 2008, from www.niaid.nih.gov/factsheets/stdsyph.htm.
19. Fitzpatrick TB, et al. Color atlas and synopsis of clinical dermatology: common and serious diseases. 3d ed. New York: McGraw-Hill, 1997:878-903.
20. Queensland Health. Queensland clinical practice guidelines for advanced sexual and reproductive health nursing officers. Public Health Service Branch. Queensland Government. 2007.