SYPHILIS

This chapter from the Canadian Guidelines on Sexually Transmitted Infections 2006 Edition has undergone revisions and has been updated as of October 2007. The chart below summarizes the most significant changes made to the chapter and cross-references the corresponding page numbers in the current hard copy version of the guidelines.

Section	Page	Current Wording/Problem	Update/Clarification
Numerous		Due to the emergence of congenital syphilis in some regions in Canada where heterosexual syphilis outbreaks have been reported, the Syphilis chapter has been extensively revised.	Changes are too numerous to list, please print the entire chapter and discard/disregard previous version.

SYPHILIS

Etiology

- Caused by *Treponema pallidum* subsp*. pallidum.*
- *T. pallidum* subsp. *pallidum* causes venereal syphilis, *T. pallidum* subsp. *endemicum* causes endemic syphilis (bejel), *T. pallidum* subsp. *pertenue* causes yaws and *T. carateum* causes pinta.

Epidemiology

- Infectious syphilis (primary, secondary and early latent stages) is the least common of the three nationally reportable bacterial sexually transmitted infections (STIs).[1]
- After achieving rates of 0.4–0.6/100,000 from 1994 to 2000, rates of infectious syphilis started to rise. The preliminary figures for 2006 show rates of 4.6/100,000.[1,2]
- The rate of infectious syphilis is increasing in both males and females, but more so in males. In recent years, localized outbreaks of infectious syphilis have been reported in a number of locations worldwide[3, 4] and in Canada, including Vancouver, Yukon, Calgary, Edmonton, Winnipeg, Toronto, Ottawa, Montreal and Halifax.[2, 5–7]
- Most of the outbreaks have been in men who have sex with men (MSM) and others related to sex trade but some have been locally acquired infections in heterosexual persons not fitting into one of these categories. Some large outbreaks among MSM primarily in the United States have been associated with the acquisition of anonymous sex partners through the Internet.[8]
- Based on data from British Columbia, Alberta and Yukon, Aboriginal people in these two provinces and one territory are disproportionately affected by the STI epidemic. It is estimated that Aboriginal people in these geographic areas account for over 25% of infectious syphilis cases and yet comprise about 4% of the Canadian population. This exists in the context of social and health inequities.
- 5 cases of congenital syphilis were reported in British Columbia between 1994 and 2003.[9] In 2005 and 2006, 9 babies were born in Alberta with congenital syphilis.[7] Nationally, 2 congenital cases or less a year were reported in the decade before 2005. Preliminary reports indicate that there were 8 cases each in 2005 and 2006.[10]
- Syphilis, as with other STIs, increases the risk of acquisition and transmission of HIV.

Transmission

- The primary mode of transmission is by vaginal, anal and oral sexual contact.[11]
- Kissing, sharing of needles and injection equipment, blood transfusion and accidental inoculation have rarely been reported as routes of transmission.
- Primary, secondary and early latent stages are considered infectious, with an estimated risk of transmission per partner of around 60%.[12] Early latent syphilis is considered infectious because of the 25% chance of relapse to secondary stage.[13]
- The majority of infants with congenital syphilis are infected in utero, but they can also be infected by contact with an active genital lesion at the time of delivery. The risk of transmission in untreated women is 70-100% with primary or secondary syphilis, 40% with

early latent syphilis and 10% in late latent stages in pregnancy.[14,15] About 40% of pregnancies in women with infectious syphilis results in fetal demise.[16]

- Breastfeeding by mothers with primary or secondary lesions of syphilis carries a theoretical risk of transmission of syphilis to the baby.

Prevention

- Sexual activity of any mucosal type - oral, anal or genital – can be a mode of transmission for syphilis. It is important that health professionals accurately communicate the risks associated with various sex acts to sexually active patients, including the risk of transmission via oral sex and ensure the use of a barrier method for oral sex (i.e., although the risk of STI transmission is lower via oral sex than vaginal or anal sex, many STIs, including syphilis can be transmitted through unprotected oral sex).
- Asymptomatic patients presenting with concerns about STIs and/or birth control should be given information on the efficacy of barrier methods in preventing STI/HIV transmission and provided safer sex counselling (see Primary Care and Sexually Transmitted Infections chapter).
- Persons presenting with concerns about syphilis (or STI/HIV) infection provide an important opportunity for education and encouragement for consistent practice of risk reduction behaviours. These practices include, but are not limited to, sexual abstinence, reducing the number of sexual partners and proper and consistent use of barrier methods (see Primary Care and Sexually Transmitted Infections chapter).
- Identify barriers to prevention practices and the means to overcome them (see Primary Care chapter).
- In patients with confirmed syphilis infection, patients and their partners should abstain from unprotected intercourse until treatment of both partners is complete.
- Syphilis can also be passed from mother to child during pregnancy and therefore routine prenatal screening for syphilis is an important means of prevention (refer to Diagnosis section under *Special considerations in pregnant women and newborn infants* in the current chapter).
- In cases where a child is born to a mother who was diagnosed with syphilis in pregnancy, and where the child is placed under the care of child protection services, medical information about the mother's diagnosis may be critical to the ongoing protection and monitoring of the infant's health. It is important to facilitate the collection and disclosure of relevant health information, in accordance with provincial/territorial requirements, in order to allow appropriate follow-up care (refer to Special considerations section in the current chapter under *Pregnancy*).

Manifestations

Table 1. Manifestations[11]

Stage	Clinical manifestations	Incubation period
Primary	Chancre, regional lymphadenopathy	3 weeks (3–90 days)
Secondary	Rash, fever, malaise, lymphadenopathy, mucus lesions, condyloma lata, alopecia, meningitis, headaches, uveitis, retinitis	2–12 weeks (2 weeks– 6 months)
Latent	Asymptomatic	Early: <1 year Late: ≥1 year
Tertiary		
Cardiovascular syphilis	Aortic aneurysm, aortic regurgitation, coronary artery ostial stenosis	10–30 years
Neurosyphilis	Ranges from asymptomatic to symptomatic with headaches, vertigo, personality changes, dementia, ataxia, presence of Argyll Robertson pupil	<2 years–20 years
Gumma	Tissue destruction of any organ; manifestations depend on site involved	1–46 years (most cases 15 years)
Congenital		
Early	2/3 may be asymptomatic. Fulminant disseminated infection, mucocutaneous lesions, osteochondritis, anemia, hepatosplenomegaly, neurosyphilis	Onset <2 years
Late	Interstitial keratitis, lymphadenopathy, hepatosplenomegaly, bone involvement, anemia, Hutchinson's teeth, neurosyphilis	Persistence >2 years after birth

Diagnosis

Risk factors

A diagnosis of syphilis should be considered in anyone with signs or symptoms compatible with syphilis and also in the following individuals:

- Those who have had contact with a known case of syphilis.
- MSM.
- Sex workers.
- Those with street involvement/homeless.
- Injection drug users.
- Those with multiple sexual partners.
- Those with a history of syphilis, HIV and other STIs.
- Those originating from or having sex with an individual from a country with a high prevalence of syphilis; it should be noted that screening for syphilis (using a non-treponemal test) is routinely performed in all immigration applicants to Canada who are older than 15 years.
- Sexual partners of any of the above.

Individuals of aboriginal ethnicity are disproportionately affected by syphilis in some geographic areas of Canada, particularly in some areas experiencing outbreaks of infectious syphilis; the decision to screen or re-screen Aboriginal persons for syphilis should be made in the context of local epidemiology.

Symptoms and signs

- Current or past history of lesions or rash (See Manifestations, above).
- A high proportion of individuals fail to recall a primary chancre.[11]
- Signs and symptoms may be modified in the presence of HIV co-infection.[17]

Special considerations in pregnant women and newborn infants

- Given the resurgence of syphilis in Canada, universal screening of all pregnant women continues to be important and remains the standard of care in most jurisdictions.
- Screening should ideally be performed in the first trimester and repeated at 28-32 weeks and again at delivery in women at high risk of acquiring syphilis (See Risk Factors, above) or in areas experiencing heterosexual outbreaks of syphilis.
- Any woman delivering a stillborn infant at $\geq$ 20 weeks gestation should be screened for syphilis.
- No newborn should be discharged from hospital prior to confirmation that either the mother or newborn infant has had syphilis serology undertaken during pregnancy or at the time of labour or delivery.
- Infants presenting with signs or symptoms compatible with early congenital syphilis should be tested for syphilis.

Laboratory diagnosis

- The interpretation of syphilis serology should be made in conjunction with a colleague experienced in this area (see Table 2).

- Every attempt should be made to obtain and document prior history of treatment for syphilis and prior serologic results in order to avoid unnecessary retreatment.

Specimen collection

- Dark-field microscopy, DFA/IFA or PCR (For more information on available tests, please contact your local laboratory). To visualize *T. pallidum* from chancres of primary syphilis and some lesions of secondary syphilis (e.g., condyloma lata).
- Dark-field microscopy testing for *T. pallidum* is not reliable for oral/rectal lesions, as non-pathogenic treponemes may be present. Instead, direct fluorescent antibody test for *T. pallidum* should be used on such specimens.
- Polymerase chain reaction (PCR) is available only at specialized laboratories, including the National Microbiology Laboratory.

Serology

- Screening for syphilis has traditionally involved the use of non-treponemal tests (NTT) such as rapid plasma reagin (RPR), followed by confirmatory treponemal tests if the NTT is reactive. However, in patients with suspected primary syphilis or late latent syphilis, the NTT may be non-reactive, and it is then appropriate to add a treponemal test to the initial screen or, in the case of primary syphilis, to repeat the NTT after 2–4 weeks. In regions experiencing outbreaks of syphilis, it may be appropriate to screen at baseline with both non-treponemal and treponemal tests.
- The introduction of treponemal tests for IgG/IgM antibodies, such as the treponemal enzyme immunoassay **(**EIA), may provide a more sensitive screening test for syphilis. Although EIA is highly sensitive, the test can lack specificity therefore if the treponemal-specific ELISA is positive, confirmation by a second treponemal-specific test is required (e.g. TP-PA, MHA-TP, FTA-ABS).
- Non-treponemal tests include RPR, venereal disease research laboratory (VDRL) and the toluidine red unheated serum test (TRUST).
- Non-treponemal antibody titres usually correlate with disease activity and are used to monitor response to treatment and assess for reinfection.
- Treponemal tests include the *T. pallidum* particle agglutination (TP-PA), fluorescent treponemal antibody absorbed (FTA-ABS) and EIA to detect IgG and/or IgM antibodies.
- Treponemal tests (e.g. FTA-ABS, MHA-TP and EIA) usually remain reactive for life regardless of treatment, although 15–25% will serorevert if the patient is treated during the primary stage.

Table 2. Guide to interpretation of serologic tests for syphilis

Test results on blood or serum			Most likely condition
Non-treponemal test: RPR/VDRL	**Treponemal test: TP-PA**	**Treponemal test: FTA-ABS**	
NR	**NR**	**R**	Primary syphilis with compatible history/clinical findings
R *(dilutions can vary)*	**R**	**R**	Infectious syphilis (primary, secondary, early latent), especially if titre >1:8 **OR** Old treated syphilis (especially if titre <1:8) **OR** Follow-up of treated syphilis **OR** In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel
NR	**R**	**R**	Usually treated syphilis **OR** Early infection (early primary syphilis) **OR** Late latent syphilis **OR** In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel **OR** Lyme Disease
R	**NR**	**NR**	Biological false positive* *(repeat in 3–4 weeks)*

FTA-ABS = fluorescent treponemal antibody absorbed
NR = non-reactive
R = reactive
RPR = rapid plasma reagin
TP-PA = *T. pallidum* particle agglutination
VDRL = venereal disease research laboratory
*Some causes of false positive serologic tests for syphilis include certain collagen-vascular diseases, pregnancy, injection drug use, etc.

Cerebrospinal fluid

- Criteria for cerebrospinal fluid (CSF) examination include the following:
  - Presence of neurologic or ophthalmic symptoms or signs.
  - Congenital syphilis.
  - Previously treated patients who fail to achieve an adequate serologic response to treatment.
  - Tertiary syphilis.[18]
  - HIV patients with neurologic symptoms or signs, late latent syphilis, RPR ≥1:32 dilutions, CD4 <350 cells/μL or treated syphilis with suboptimal decline in VDRL/RPR titre; some experts recommend CSF examination in all HIV-infected individuals.[19]
  - Some experts recommend CSF examination in all patients with RPR ≥1:32 dilutions.[19]
- CSF should be tested for cell count and differential, protein, VDRL and/or FTA-ABS.
- CSF-VDRL is highly specific but insensitive.
- CSF FTA-ABS is highly sensitive but non-specific for neurosyphilis; a negative CSF FTA-ABS helps to exclude a diagnosis of neurosyphilis.[18,20–22]
- The diagnosis of neurosyphilis is usually made on a combination of reactive serologic results, abnormalities of CSF cell count or protein or a reactive CSF-VDRL with or without clinical manifestations.

Management

Primary and secondary syphilis

- Attempt to obtain material from primary or secondary lesions for dark-field microscopy and/or DFA/IFA for *T. pallidum.*
- Ulcers should also be tested for herpes simplex virus and/or chancroid (if epidemiologically appropriate) and/or lymphogranuloma venereum (if epidemiologically appropriate).
- Serology should include both treponemal and non-treponemal tests to establish the diagnosis. Note that both non-treponemal and treponemal tests may be negative in early primary syphilis. Serology should be repeated in 2–4 weeks if they are dark-field or DFA/IFA negative and/or no treatment has been given. If follow-up cannot be assured, it may be appropriate to treat presumptively for primary syphilis.

Latent syphilis

- Serology: both treponemal and non-treponemal tests to establish the diagnosis; note that a negative non-treponemal test does not rule out the diagnosis of latent syphilis.
- All patients should undergo a physical examination, including neurologic examination, to evaluate for the presence of signs of tertiary syphilis. Chest x-ray may be appropriate to evaluate for the presence of cardiovascular syphilis (e.g., aneurysm of ascending aorta).
- Lumbar puncture may be appropriate (See Cerebrospinal Fluid, above).
- Treat as appropriate for stage.

Tertiary syphilis

- Serology: both treponemal and non-treponemal tests to establish the diagnosis; note that a negative non-treponemal test does not rule out the diagnosis of tertiary syphilis.
- All patients with suspected tertiary syphilis should undergo CSF examination.
  - If CSF is not compatible with a central nervous system (CNS) infection, treat as for late latent syphilis.
  - If CSF is compatible with a CNS infection, treat as for neurosyphilis.

Congenital syphilis

- Obtain venous samples from both mother and baby (note that cord blood is not suitable) for serology (treponemal and non-treponemal tests).
  - The interpretation of reactive antibodies in the neonate must take into consideration the maternal history, including stage of syphilis, history of treatment, and syphilis serology results.
- Placenta, neonatal nasal discharge or skin lesions may be examined by dark-field microscopy or DFA/IFA or PCR for *T. pallidum.*
- CSF examination should be performed on all infants with suspected congenital syphilis.
- Long-bone x-rays should be performed.

Treatment

- Although regimens containing daily IM procaine penicillin for 10–14 days are equally efficacious to regimens containing benzathine penicillin G, the latter are preferred because of better adherence with less frequent dosing.
- Benzathine penicillin G is available in Canada only through provincial/territorial sexually transmitted disease services, which obtain the drug from non-Canadian pharmaceutical companies through Health Canada's Special Access Program, as the drug is no longer available in Canada.
- Reports from some jurisdictions have indicated inappropriate use of short-acting benzylpenicillin (Penicillin G) (IM) for the treatment of infectious syphilis rather than the standard long-acting Benzathine penicillin G (Bicillin-LA). Practitioners, pharmacists and purchasing agents should be aware of the similar names of these two products to prevent and avoid inappropriate and inadequate treatment. Long-acting benzathine penicillin achieves detectable serum levels of penicillin for 2-4 weeks in non-pregnant adults and is required to adequately treat infectious syphilis; short acting penicillin agents are not adequate for achieving cure.[23]

Table 3. Treatment

Stage	Preferred treatment [Ψ]	Alternative treatment for penicillin-allergic patients
All **non-pregnant adults** • Primary • Secondary • Early latent (<1 year duration)	Benzathine penicillin G 2.4 million units IM as a single dose*[24-27] *[A-II; A-III for HIV-infected individuals]*	• Doxycycline 100 mg PO bid for 14 days[28,29] *[B-II]* **Alternative agents (to be used in exceptional circumstances)[†]** • Ceftriaxone 1 g IV or IM daily for 10 days[30,31] *[B-II]*
All **non-pregnant** adults • Late latent syphilis • Latent syphilis of unknown duration • Cardiovascular syphilis and other tertiary syphilis not involving the central nervous system	Benzathine penicillin G 2.4 million units IM weekly for 3 doses[32,33] *[A-II]*	• Consider penicillin desensitization • Doxycycline 100 mg PO bid for 28 days[29] *[B-II]* **Alternative agents (to be used in exceptional circumstances)[†]** • Ceftriaxone 1 g IV or IM daily for 10 days[34] *[C-III]*
All adults *Neurosyphilis*	Penicillin G 3–4 million units IV q 4 h (16–24 million units/day) for 10–14 days[33] *[A-II]*	• Strongly consider penicillin desensitization followed by treatment with penicillin • Ceftriaxone 2 g IV/IM qd x 10–14 days[33,35,36] *[B-II]*
Epidemiological treatment of sexual contacts in the preceding 90 days to primary, secondary and early latent syphilis§[‖37]	Benzathine penicillin G 2.4 million units IM as a single dose [B-II]	• See comment below on Azithromycin [‖]

[Ψ]Reports from some jurisdictions have indicated inappropriate use of short-acting benzylpenicillin (Penicillin G) (IM) for the treatment of infectious syphilis rather than long-acting Benzathine penicillin G (Bicillin-LA). Practitioners, pharmacists and purchasing agents should be aware of the similar names of these two products to prevent and avoid inappropriate and inadequate treatment. Long-acting benzathine penicillin achieves detectable serum levels of penicillin for 2-4 weeks in non-pregnant adults and is required to adequately treat infectious syphilis; short acting penicillin agents are not adequate for achieving cure.[23]
*Some experts recommend 3 weekly doses (total of 7.2 million units) of benzathine penicillin G in HIV-infected individuals.

†The efficacy data supporting the use of these agents is limited, and as such they should only be used in exceptional circumstances and when close patient follow-up is assured.
§If sexual contact is unreliable or unable to test, then epidemiological treatment should be strongly considered.

‖ ***Azithromycin:*** in light of recent reports of failure of azithromycin for the treatment of early syphilis[38] and the rapid development of azithromycin resistance in *T. pallidum*[39,40], this agent should not be routinely used as a treatment option for early or incubating syphilis unless adequate and close follow up can be ensured, and only in jurisdictions where little to no azithromycin genotypic resistance in *T. pallidum* has been demonstrated. It should be noted, however, that at the present time, very limited Canadian data on the prevalence of Azithromycin resistance in *T. pallidum* is available, with 1 of 47 specimens between 2000-2003 as compared with 4 of 9 specimens from MSM in 2004-2005 collected in Vancouver demonstrating resistance.[40]

Table 3. Treatment (continued)

Stage	Preferred treatment Ψ	Alternative treatment for penicillin-allergic patients
Pregnant women • Primary • Secondary • Early latent (<1 year duration)	Benzathine penicillin G 2.4 million units IM weekly for 1-2 doses[ΨΨ*41] *[B-II (single dose);C-III (2 doses)]*	• There is no satisfactory alternative to penicillin for the treatment of syphilis in pregnancy; insufficient data exist to recommend ceftriaxone in pregnancy • Strongly consider penicillin desensitization followed by treatment with penicillin *[A-III]*
Pregnant women • Late latent syphilis • Latent syphilis of unknown duration • Cardiovascular syphilis and other tertiary syphilis not involving the central nervous system	Benzathine penicillin G 2.4 million units IM weekly for 3 doses[42] *[B-II]*	• There is no satisfactory alternative to penicillin for the treatment of syphilis in pregnancy; insufficient data exist to recommend ceftriaxone in pregnancy • Strongly consider penicillin desensitization followed by treatment with penicillin *[A-III]*

ΨReports from some jurisdictions have indicated inappropriate use of short-acting benzylpenicillin (Penicillin G) (IM) for the treatment of infectious syphilis rather than long-acting Benzathine penicillin G (Bicillin-LA). Practitioners, pharmacists and purchasing agents should be aware of the similar names of these two products to prevent and avoid inappropriate and inadequate treatment. Long-acting benzathine penicillin achieves detectable serum levels of penicillin for 2-4 weeks in non-pregnant adults and is required to adequately treat infectious syphilis; short acting penicillin agents are not adequate for achieving cure.[23]

*Some experts recommend 3 weekly doses (total of 7.2 million units) of benzathine penicillin G in HIV-infected individuals.
§If sexual contact is unreliable or unable to test, then epidemiological treatment should be strongly considered.

¥ Given the complexity of accurately staging early syphilis, some experts recommend that primary, secondary and early latent cases in pregnancy be treated with two doses of benzathine penicillin G 2.4 million units 1 week apart; the efficacy of this regimen in preventing fetal syphilis is not known.[43]

Table 3. Treatment (continued)

Stage	*Preferred treatment* [ψ]	Alternative treatment for penicillin-allergic patients
Congenital syphilis[44]	***<1 month*** Crystalline penicillin G 50,000 units/kg IV every 12 hours for the first week of life and every 8 hours thereafter for 10 days of total therapy *[A-II]* ***Addendum:*** *Benzathine penicillin G 50,000 units/kg IM in a single dose (C-III) has been recommended by some experts for infants born to mothers with infectious syphilis:* *1. in whom adequate maternal treatment is confirmed* ***AND*** *2. where there is no concern regarding re-infection in the mother* ***AND*** *3. In infants with with no clinical or laboratory evidence of congenital syphilis* *Alternatively, meticulous follow up (e.g. monthly clinical/laboratory follow up) until clearance of passively transferred antibodies may be indicated if there is good indication that adequate maternal treatment occurred.*	
	≥1 month Crystalline penicillin G 50,000 units/kg/ IV every 6 hours for 10–14 days *[A-II]*	• If no neurologic involvement and normal CSF: benzathine penicillin G 50,000 units/kg IM (max 2.4 million units) weekly for 3 successive weeks *[B-II]* • No data are available to recommend penicillin alternatives in the case of penicillin allergy

[ψ]Reports from some jurisdictions have indicated inappropriate use of short-acting benzylpenicillin (Penicillin G) (IM) for the treatment of infectious syphilis rather than long-acting Benzathine penicillin G (Bicillin-LA). Practitioners, pharmacists and purchasing agents should be aware of the similar names of these two products to prevent and avoid inappropriate and inadequate treatment. Long-acting benzathine penicillin achieves detectable serum levels of penicillin for 2-4 weeks in non-pregnant adults and is required to adequately treat infectious syphilis; short acting penicillin agents are not adequate for achieving cure.[23]

Penicillin desensitization

- Skin testing with the major and minor determinants can reliably identify persons at high risk for penicillin reactions.
- Patients who have a positive skin test to one of the penicillin determinants can be desensitized.
- Oral desensitization is preferable to IV desensitization, as it is safer and less costly.
- Desensitization should occur in a hospital setting as serious allergic reactions, although unlikely, can occur. The whole procedure usually can be completed in 4 hours, after which the first dose of penicillin is given. After administration of the dose, the patient should be observed for at least 1 hour.

Table 4. Oral desensitization protocol for patients with a positive skin test[45]

Penicillin V suspension dose number*	Amount† units/mL	Volume administered (mL)	Units	Cumulative dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

*Interval between doses, 15 minutes; elapsed time, 3 hours and 45 minutes; cumulative dose, 1.3 million units.
†The specific amount of drug is diluted in approximately 30 mL of water and then administered orally.

Consideration for other STIs

- All patients with reactive syphilis serology should be tested for HIV, as this affects treatment and follow-up.
- Testing for other STIs, including chlamydia and gonorrhea, should be performed.
- Genital ulcers should also be tested for herpes simplex virus and/or chancroid and/or lymphogranuloma venereum, depending on epidemiologic risk.
- Immunization against hepatitis B and/or A may be indicated if not already immune.
- Discuss HPV vaccine with women as per the recommendations outlined in the Canada Communicable Disease Report, Volume 33 ACS-2, (2007) *National Advisory Committee on Immunization (NACI) statement on Human papillomavirus vaccine.*

Reporting and partner notification

- Infectious syphilis (primary, secondary and early latent syphilis) is reportable in all provinces and territories and to the Public Health Agency of Canada.
- Non-infectious syphilis (late latent, cardiovascular and neurosyphilis) may be reportable at the provincial/territorial level but is not reportable to Public Health Agency of Canada.
- All sexual or perinatal contacts within the following time periods need to be located, tested and treated if serology is reactive.

Table 5. Partner notification

Stage of syphilis	Time period
Primary syphilis	3 months prior to the onset of symptoms
Secondary syphilis	6 months prior to the onset of symptoms
Early latent	1 year prior to the diagnosis
Late latent	Assess marital or other long-term partners and children as appropriate
Congenital	Assess mother and her sexual partner(s)
Stage undetermined	Assess/consult with a colleague experienced in syphilis management

Follow-up

- In the absence of a test of cure, non-treponemal tests (NTTs) should be monitored until they are seronegative or at a stable low titre (e.g., 1:4 dilutions).[46]
- See Table 6 for a guide to the monitoring of NTTs.
- See Table 7 for a guide to adequate serologic response (in NTT: e.g., RPR).[47]

Table 6. Monitoring of serologic tests and other follow up

Primary, secondary, early latent	(1), 3, 6, 12 months after treatment
Late latent, tertiary	12 and 24 months after treatment
Neurosyphilis	6, 12 and 24 months after treatment Patients with CSF abnormalities require follow up CSF at 6 monthly intervals until normalization of CSF parameters (see notes below). Other clinical follow up may be indicated on a case by case basis.
HIV-infected (any stage)	(1), 3, 6, 12 and 24 months after treatment and yearly thereafter
Pregnant women treated for infectious syphilis in pregnancy	Repeat NTT dependent on stage of syphilis; in areas with high prevalence/outbreaks of syphilis and in women at high risk for re-infection, NTT should be done monthly until delivery.
Babies born to mothers treated for infectious syphilis during pregnancy*	NTT and TT at 0, 3 and 6 months after birth; repeat non-treponemal and treponemal tests at 12 - 18 months if remain reactive at 6 months. All babies should be clinically assessed at birth and monthly for congenital syphilis either by or in conjunction with a specialist pediatrician; additional investigations may include long bone x-rays and CSF examination.
Babies born to mothers treated for non-infectious syphilis during pregnancy*	NTT and TT at 0 and 6 months after birth; repeat non-treponemal and treponemal tests at 12 - 18 months if remain reactive at 6 months.
Babies with congenital syphilis*	NTT and TT at 0, 3, 6, 12 -18 months after birth. Additional investigations at baseline should include long bone x-rays and CSF examination. All babies should be clinically assessed at birth and at regular intervals either by or in conjunction with a specialist pediatrician.

*NTT titres should decline by 3 months of age and be non-reactive by 6 months if the infant was not infected. If the titres are stable or increase after 6–12 months of age, the child should be evaluated (including CSF examination) and treated as for congenital syphilis. Passively transferred treponemal antibodies can be present in an infant up to 15 months; a reactive treponemal test after 18 months is diagnostic of congenital syphilis.
(1) Some experts recommend follow up testing at 1 month after treatment to ensure that non-treponemal test titre is not rising.

Table 7. Adequate serologic response

Primary	2-tube* drop at 6 months, 3-tube drop at 12 months, 4-tube drop at 24 months
Secondary	3-tube and 4-tube drop at 6 and 12 months, respectively
Early latent	2-tube drop at 12 months

*2-tube drop=four-fold drop, e.g., change from 1:32 dilutions to 1:8 dilutions.

- Note that the NTT may revert to non-reactive after treatment or remain at a low steady level (sero-fast); repeat testing is not required if the baseline or follow-up NTT becomes non-reactive, except in HIV-infected individuals.
- A rising NTT after treatment may indicate treatment failure or reinfection. If treatment failure is suspected, further investigation, including CSF examination, may be indicated.
- Patients with neurosyphilis and abnormal CSF examinations should have a lumbar puncture repeated at 6-month intervals after completion of treatment until CSF parameters normalize. CSF pleocytosis is generally the first measure of improvement and should occur over about 6 months.[48] Elevated protein levels, if present, will begin to decline during the first 6 months but can take up to 2 years to return to normal.[49] CSF protein may decline more slowly in patients who are neurologically abnormal compared with those who are neurologically normal.[50] The CSF-VDRL titre should decline (four-fold within a year) if it is initially high, but it may take years to revert to negative.[48] A persistent, low CSF-VDRL titre after a course of treatment may warrant retreatment, but if CSF pleocytosis and elevated protein levels have resolved and serum VDRL titre has not risen, additional treatment is unlikely to be beneficial.[51] All CSF lab parameters normalize more slowly in patients co-infected with HIV.[50] The possibility of treatment failure should be considered if there is clinical progression, increase in RPR/VDRL by ≥2 dilutions or CSF pleocytosis fails to resolve; treatment options for patients with treatment failure should be discussed with a colleague experienced in this area.

Special considerations

HIV infection

- Persons co-infected with HIV may require a longer course of treatment, as well as closer and longer follow-up.

Pregnancy[43]

- All women newly diagnosed with syphilis during pregnancy should receive treatment appropriate to their stage of disease, with the exception of secondary syphilis in late pregnancy, where despite the administration of the recommended penicillin regimen as many as 14% will have a fetal death or deliver infants with clinical evidence of congenital syphilis.[52–54] Some experts recommend that primary, secondary and early latent cases in pregnancy be treated with two doses of benzathine penicillin G 2.4 million units 1 week apart; the efficacy of this regimen in preventing fetal syphilis is not known.[43]

- Retreatment during pregnancy is not necessary unless there is clinical or serologic evidence of new infection (four-fold rise in a non-treponemal test titre) or history of recent sexual contact with early syphilis.
- Erythromycin is the least effective agent for the treatment of syphilis and does not penetrate the CSF or placental barrier well; it is therefore not recommended in pregnancy.[55,56]
- If the mother is >20 weeks gestation, an ultrasound should be performed and she should be managed with a obstetrician/maternal-fetal medicine specialist; if fetal abnormalities are identified, the mother should be hospitalized for treatment and fetal monitoring.[57]
- All babies should be assessed at delivery by a pediatrician or pediatric specialist (e.g. infectious diseases), and if a maternal non-penicillin regimen was used, consideration should be given to treating the baby empirically for congenital syphilis.
- In cases where a child is born to a mother who was diagnosed with syphilis in pregnancy, and where the child is placed under the care of child protection services, medical information about the mother's diagnosis may be critical to the ongoing protection and monitoring of the infant's health. It is important to facilitate the collection and disclosure of relevant health information, in accordance with provincial/territorial requirements, in order to allow appropriate follow-up care.

Congenital syphilis[58]

- Infected infants are frequently asymptomatic at birth and may be seronegative if maternal infection occurred late in gestation.
- Infants should be treated at birth:
  - If symptomatic.
  - If the infant's non-treponemal titre is at least four-fold (2 tubes) higher than the mother's.
  - If maternal treatment was inadequate, did not contain penicillin, is unknown or occurred in the last month of pregnancy, or if maternal serologic response is inadequate.
  - If adequate follow-up of the infant cannot be ensured.

Jarisch-Herxheimer reaction[59]

- Patients should be made aware of this possible reaction to treatment, especially with penicillin.
- An acute febrile illness with headache, myalgia, chills, rigours generally occurring within 8–12 hours and resolving within 24 hours.
- Common in early syphilis, but usually not clinically significant unless there is neurologic or ophthalmic involvement or in pregnancy where it may cause fetal distress and premature labour.
- Not a drug allergy.
- Can be treated with antipyretics.
- Steroids may be indicated for the management of severe reactions but should be used in consultation with a colleague experienced in this area.

Children

- Sexual abuse needs to be considered when syphilis is found in children beyond the neonatal period. Consultation with a colleague experienced in the management of such cases should be sought (see Sexual Abuse in Peripubertal and Prepubertal Children chapter).
- Reporting Sexual abuse:
  Sexual abuse of children must be reported to the local child protection agency. Local public health authorities may be helpful in evaluating both the source of the infection and potential transmission in the community.
- Whenever possible, it is strongly recommended that the child be evaluated at or in conjunction with a referral centre (see Appendix F and G).
- All persons named as suspects in child sexual abuse cases should be located and clinically evaluated; prophylactic treatment may or may not be offered and the decision to treat or not should be based on history, clinical findings and test results (see *Sexual Abuse in Peripubertal and Prepubertal Children* chapter).

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