PRACTICE POINT

Congenital syphilis: No longer just of historical interest

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The majority of paediatricians and family physicians in practice in Canada today have never seen a case of congenital syphilis. However, there have been outbreaks of syphilis across Canada since 2001, such that the incidence of syphilis in Canada in 2007 was projected to be almost 10-fold compared with what it was in 1994 to 2000 [1]-[3]. The initial increase in incidence was concentrated in men who have sex with men, but heterosexual transmission in inner-city populations now accounts for a large percentage of cases in some provinces. The incidence of syphilis in 2007 was highest in British Columbia and Alberta, followed by Quebec and Ontario [2]. This has led to an increase in reported congenital cases from approximately two per year to 10 per year nationally [1][4]; it is likely that other cases have been missed because infants are asymptomatic or the diagnosis has not been considered.

When should syphilis be suspected in a pregnant woman?

Syphilis is usually acquired by vaginal, anal or oral sex with a person who was infected with syphilis within the preceding year. Rarely, acquisition occurs by kissing, blood transfusion, sharing of needles, accidental inoculation or direct contact with an infected lesion [5]. Many infected persons have no distinctive clinical manifestations that lead to a diagnosis before progression to asymptomatic latent disease. Therefore, all pregnant women must be assumed to be at risk.

The risk of vertical transmission depends primarily on the stage of maternal syphilis, with the risk being 70% to 100% if the mother has untreated primary or secondary syphilis during pregnancy, 40% if she has early latent syphilis (as she remains at risk of reactivation) and less than 10% if she has late latent syphilis. The staging of maternal syphilis is complex and includes a combination of history, physical examination, epidemiological features, direct tests from lesions and serological tests; the reader should refer to other sources for details [1]. The majority of infants with congenital syphilis are infected in utero after the fourth month of gestation [5], but infection can occur as early as nine weeks' gestation [6] or via contact with an active genital lesion at the time of delivery. Syphilis serology should routinely be performed at the first prenatal visit, followed by appropriate maternal counselling and therapy, if reactive [1]. Rescreening should occur at 28 to 32 weeks' gestation and at delivery in high-risk women, including women who originate from a country with a high prevalence of syphilis. Routine rescreening should also be considered in areas experiencing outbreaks of heterosexual syphilis [1]. If syphilis serology was not performed during pregnancy, newborns should not be discharged from hospital until maternal serology has been drawn and follow-up of results has been arranged. If the cause is not known for a hydropic or stillbirth newborn, the mother should be screened for syphilis postpartum.

How should syphilis serology be interpreted?

Syphilis serological tests include a nontreponemal test, such as a rapid plasma reagin (RPR) test or a venereal disease research laboratory (VDRL) test, currently used in Canada only for testing of cerebrospinal fluid (CSF), and a treponemal test that detects treponemal-specific antibodies including fluorescent treponemal antibody absorption (FTA-ABS), *Treponema pallidum* particle agglutination, microhemagglutination for *T pallidum*, enzyme immunoassay (EIA) and line-blot immunoassay, such as INNO-LIA (Innogenetics, Belgium), with interpretation as shown in Tables 1 and 2.

TABLE 1
Guide to interpretation of serological tests for syphilis

Test results on blood or serum			
Initial screen: nontreponemal test – RPR	**Confirmatory assay: treponemal test – TP-PA**	**Confirmatory assay: treponemal test – FTA-ABS**	**Most likely condition**

Nonreactive	Nonreactive	Reactive	Primary syphilis with compatible history/clinical findings
Reactive (dilutions can vary)	Reactive	Reactive	Syphilis, any stage (note that it is more likely to be infectious if the RPR titre is 32 dilutions or greater [dilations can vary]) OR old treated syphilis OR follow-up of treated syphilis OR in persons from endemic countries, yaws (eg, Caribbean), pinta (eg, Central America) or bejel OR Lyme disease
Nonreactive	Reactive	Reactive	Usually treated syphilis OR early infection (early primary syphilis) OR late latent/tertiary syphilis OR in persons from endemic countries, yaws (eg, Caribbean), pinta (eg, Central America) or bejel OR Lyme disease
Reactive	Nonreactive	Nonreactive	False positive*

**Some causes of false-positive serological tests for syphilis include certain conditions such as collagen-vascular diseases, pregnancy, injection drug use, Lyme disease, etc; or false-positive inherent to the kit or test technique. FT-ABS Fluorescent treponemal antibody absorption; RPR Rapid plasma regain; TP-PA* Treponema pallidum *particle agglutination.*

Adapted from reference [1], and reproduced with the permission of the Minister of Public Works and Government Services, 2009

TABLE 2
Guide to interpretation of serological tests for syphilis

Test results on blood or serum			
Initial screen: treponemal test – syphilis EIA	**Nontreponemal test – RPR result and titre**	**Confirmatory test (if performed)*: treponemal test – TA_PA, syphilis INNO-LIA**	**Most likely condition / recommended action**
Negative	Not performed	Not performed	Not a case Repeat serology† if at risk for syphilis
Borderline / indeterminate	Nonreactive	Negative or indeterminate	Repeat serology† because there may be early seroconversion If repeat serology remains unchanged, this is not a case of syphilis
Borderline / indeterminate	Nonreactive	Reactive/positive	Early primary syphilis OR late latent/tertiary syphilis OR previously treated syphilis OR in persons from endemic countries, yaws (eg, Caribbean), pinta (eg, Central America) or bejel OR Lyme disease If laboratory does not perform confirmatory testing, then repeat serology† because there may be early seroconversion. In this instance, if repeat serology remains unchanged, this is not a case of syphilis
Positive	Reactive (dilutions can vary) OR nonreactive	Negative	False positive‡ If laboratory does not perform confirmatory testing, then interpretation is early primary syphilis OR late latent/tertiary syphilis OR previously treated syphilis OR in persons from endemic countries, yaws (eg, Caribbean), pinta (eg, Central America) or bejel OR Lyme disease
Positive	Reactive (dilutions can vary)	Indeterminate	Repeat serology† to help determine whether early primary syphilis OR late latent/tertiary syphilis OR previously treated syphilis OR in persons from endemic countries, yaws (eg, Caribbean), pinta (eg, Central America) or bejel OR Lyme disease If repeat serology is unchanged, this is likely to be a false positive‡ If laboratory does not perform confirmatory testing, then interpretation is as follows: syphilis, any stage (note that it is more likely to be infectious if the RPR titre is 32 dilutions or greater [dilations can vary]) OR old treated syphilis OR follow-up of treated syphilis OR in persons from endemic countries, yaws (eg, Caribbean), pinta (eg, Central America) or bejel OR Lyme disease
Positive	Nonreactive	Indeterminate	Repeat serology† to help determine whether early primary syphilis OR late latent/tertiary syphilis OR previously treated syphilis OR in persons from endemic countries, yaws (eg, Caribbean), pinta (eg, Central America) or bejel OR Lyme disease If repeat serology is unchanged, this is likely to be a false positive‡

			If laboratory does not perform confirmatory testing, then interpretation is as follows: early primary syphilis OR late latent/tertiary syphilis OR previously treated syphilis OR in persons from endemic countries, yaws (eg, Caribbean), pinta (eg, Central America) or bejel OR Lyme disease
Positive	Nonreactive	Reactive/positive	Early primary syphilis OR late latent/tertiary syphilis OR previously treated syphilis OR in persons from endemic countries, yaws (eg, Caribbean), pinta (eg, Central America) or bejel OR Lyme disease
Positive	Reactive (dilutions can vary)	Reactive/positive	Syphilis, any stage (note that it is more likely to be infectious if the RPR titre is 32 dilutions or greater [dilations can vary]) OR old treated syphilis OR follow-up of treated syphilis OR in persons from endemic countries, yaws (eg, Caribbean), pinta (eg, Central America) or bejel OR Lyme disease

*INNO-LIA is manufactured by Innogenetics, Belgium. *Confirmatory tests are not performed in all jurisdictions. Syphilis testing algorithms vary across Canada, and it is, therefore, recommended that you check with your laboratory regarding local testing protocols; †Serology is typically repeated two to four weeks after the initial test to observe the rise in the rapid plasma reagin (RPR) tire to detect enzyme immunoassay (EIA)/confirmatory test conversion; ‡Some causes of false-positive serological tests for syphilis included certain conditions susch as collagen-vascular diseases, pregnancy, injection drug use, Lyme disease, etc, or false-positive reactions inherent to the kit or testing technique. TP-PA* Treponema pallidum *particle agglutination.*
Adapted from a Public Health Agency of Canada draft. Readers are referred to the Public Health Agency of Canada – sexually transmitted infections pamphlet. Guidelines are available at <http://www.phac-aspc,gc,ca/std-mts/sti_2006/pdf-510_Syphilis.pdf. (Version current at March 18, 2009)

Two screening approaches for syphilis are used in Canada. Most jurisdictions use RPR as an initial screen, and confirm a reactive result with a treponemal test. Some jurisdictions have introduced EIA as the initial screen, with confirmation by another treponemal test because EIA has a higher sensitivity and specificity than RPR. Obtaining RPR titres is still necessary if the EIA is positive because they are used for staging infection, following the response to treatment and diagnosing reinfection. Confirmed treponemal tests are fairly specific for syphilis, but can also occur with nonvenereal treponemal diseases (Tables 1 and 2).

Which women with reactive treponemal tests have been adequately treated before pregnancy?

The treponemal test usually remains reactive for life unless treatment was administered very early in the infection; therefore, a decrease in the RPR titre must be monitored. The expected RPR titre decline with adequate therapy is a fourfold drop (eg, from 1:32 dilutions to 1:8 dilutions) at six months, an eightfold drop at 12 months and a 16-fold drop at 24 months with primary syphilis; an eightfold drop at six months and a 16-fold drop at 12 months with secondary syphilis; and a fourfold drop at 12 months with early latent syphilis [1]. The RPR may eventually revert to nonreactive after treatment or remain at a low steady level (serofast). Even if these criteria are fulfilled, maternal RPR should be repeated at appropriate intervals during the pregnancy if reinfection is thought to be a risk. In the common scenario in which a woman has a reactive treponemal test and a nonreactive RPR during pregnancy, with no history of treatment and no evidence of early primary syphilis, she should be treated for late latent syphilis and it should be assumed that there is some risk of vertical transmission.

What is the management of an infant born to a mother with a reactive treponemal test who has not been adequately treated for syphilis or was treated during pregnancy?

If maternal RPR titres did not decline as described above, if follow-up titres were not obtained or if maternal reinfection is a possibility, infants should be considered to be at risk for congenital syphilis. The majority of infants with early congenital syphilis (defined as syphilis diagnosed in the first two years of life) are asymptomatic at birth, so diagnosis relies on positive laboratory and/or radiographic findings. Table 3 outlines the clinical features of congenital syphilis and Table 4 outlines the suggested management as determined by the estimated risk of congenital syphilis. As a general guide, infant RPR titres will decline by three months of age and be nonreactive by six months of age in the absence of congenital syphilis. The expected course of treponemal test results, such as EIA, is less clear, but passive antibodies from other infections usually clear by 12 months of age and always clear by 18 months of age. In addition to the investigations mentioned in Table 4, any skin lesions, nasal discharge, placental lesions

or the umbilical cord can be examined for treponemes using darkfield microscopy or direct fluorescent treponemal antibody test after consultation with the local laboratory. Molecular assays, such as polymerase chain reaction, may be available as a research or adjunctive diagnostic tool.

TABLE 3
Common features of congenital syphilis*

Feature	Usual timing	Details
Spontaneous abortion/ stillbirth/ hydrops fetalis	Any gestation	Occurs in approximately 40% of cases if syphilis acquired during pregnancy, with risk being highest for first-trimester infection
Necrotizing funisitis	At birth	Umbilical cord looks like a 'barbershop pole' – rare but pathognomonic finding if present
Rhinitis and/or snuffles	Often first manifestation	Occurs in approximately 40% of cases
Rash	Onset in first eight weeks	Occurs in approximately 50% of cases – usually diffuse maculopapular rash but can also have desquamation alone, vesicular, bullous, papulosquamous or mucosal lesions
Hepatomegaly/splenomagaly	Onset in first eight weeks	Occurs in approximately 20% of cases and may persist for years
Lymphadenopathy		Occurs in approximately 5% of cases
Neurosyphilis	Can be present at birth or can be delayed	Occurs in approximately 50% of cases – usually asymptomatic
Musculoskeletal involvement	Onset in first week with permanent bony changes eventually developing	Osteochondritis or perichondritis, seen initially radiographically (25% of cases) and later as pseudoparalysis, which can be confused with child abuse as there are both bony and of tissue limb changes. Later develop frontal bossing, poorly developed maxillas, saddle nose, winged scapulas and sabre shins Recurrent arthropathy and painless knee effusions (Clutton's joints) occur after two years of age
Hematological abnormalities	Present at birth or can be delayed	Anemia, thrombocytopenia and other changes associated with hematological malignancies
Interstitial keratitis	Age: 2-20 years	
Hutchinson's teeth	When permanent dentition erupts	Upper central and lateral incisors widely spaced and shaped like screwdrivers
Mulberry molars	Age: 13-19 months	First molars have dwarfing of the cusps and hypertrophy of the enamel surrounding the cusp, giving it the appearance of a berry
Eighth nerve deafness (sensory neurodeafness)	Age: 10-40 years	

**Rarer features are meningitis, chorioretinitis, nephritic syndrome and paroxysmal cold hemoglobinuria*

TABLE 4
Management of infants born to women with reactive treponemal tests (TTs) during pregnancy*

Scenario	Baseline and monthly assessment for signs or symptoms for congenital syphilis for the first three months	Syphilis serological tests (RPR and TT) with clinical assessment each time†	Long-bone radiographs, complete blood cell count and differential, and sampling of CSF for cell count and differential, glucose, protein and VDRL, with a low threshold for doing ophthalmological and audiological assessments	Treatment for congenital syphilis
Mother has well-documented history of adequate treatment of any stage of syphilis before pregnancy, with no rise in her RPR titre during the pregnancy and no known risk factors for reinfection	No	No	No	No
Mother was treated for primary, secondary or early latent syphilis during pregnancy more than four weeks before delivery, with adequate fall in her RPR titres and no evidence of relapse or reinfaction	Yes	0, 3, 6 and 18 months	No	No
Mother was treated for late latent syphilis anytime during or following pregnancy‡	No	0, 6 and 18 months of age	No	No
Mother had untreated primary or secondary syphilis during pregnancy, treponemes are detected on direct examination of specimens from infant, infant's RPR titre is fourfold or greater (higher than the mother's at birth), or there is a fourfold rise in the infant tire, OR child has any findings compatible with congenital syphilis at any age, OR infant has a reactive RPR (and TT) at 12 months of age or a reactive TT (confirmed with a second type of TT) at 18 months of age	Yes	0, 3, 6 and 18 months of age	Yes	Yes
Mother was treated for primary, secondary or realy latent syphilis within four weekds before delivery, or was treated with an antibiotic other than penicillin, OR mather was treated for primary, secondary or early latent syphilis before or during the pregnancy and her RPR titre did not show the expected decline or inadequate time has passed to assess the decline	Yes	If treated for congenital syphilis, do at 0, 3, 6 and 18 months of age; if not treated, also do at 1, 2, 12 months of age	Yes	Usually§
Mother was treated for primary, secondary or early latent syphilis before pregnancy, but there are doubts about the adequacy of therapy or the possibility of reinfection, OR mother was treated for primary, secondary or early latent syphilis before or during the pregnancy and her follow-up RPR was not obtained, OR mother was treated for any type of syphilis during pregnancy but long-term infant follow-up cannot be assured	Yes	If treated for congenital syphilis, do at 0, 3, 6 and 18 months of age; if not treated, also do at 1, 2 and 12 months of age	Depends on risk, but mandatory if mother had primary, secondary or early latent syphilis and follow-up is not likely to occur, or if clinical or serological findings are abnormal	Depends on risk and on results of assessments¶

Infant has a reactive RPR (and TT) at six months of age	NA	Depends on timing of last serology	Yes	Usually**

**The Table assumes the maternal reactive TT result was known at or near the time of delivery. Follow-up should be performed at comparable intervals if the problem is recognized several months later; †Rapid plasma regain (RPR) and TTs should be repeated at recommended intervals until at least six months of age because false-negative results could occur at zero months from transmission at delivery or at three months from partial treatment. Testing at 12 months of age or 18 months of age can be omitted if RPR and TT are both nonreactive at six months of age; ‡Late latent syphilis implies the mother was infected more than one year before pregnancy. If there is any doubt about the stage of maternal infection, it should be assumed she may have infectious syphilis (primary, secondary or early latent), which leads to more aggressive infant follow-up; §May choose to follow closely if all investigations are normal and infant follow-up can be assured, but treatment for congenital syphilis would be the preferred option because the risk is significant; ¶If it seems likely that the mother was adequately treated, the risk of maternal reinfection is low, and infant follow-up can be assured, or of the mother had late latent syphilis, serological follow-up is sufficient. If any of these criteria are not met, full evaluation and treatment should be considered; **Assuming all assessments are normal, this infant may not have congenital syphilis. It is possible that the reactive RPR is passive, but treatment would be the preferred option because of the significant chance that the infant has congenital syphilis. CSF Cerebrospinal fluid; NA Not applicable, VDRL Venereal disease research laboratory*

Interpretation of infant CSF results is not standardized, and it is common to obtain a bloody CSF, so the results must be interpreted in the context of the risk of congenital syphilis and the results of other investigations. CSF white blood cell counts ranging from 5×106/L to 20×106/L and CSF protein ranging from 0.45 g/L to 1.0 g/L are considered normal by different experts [7]. CSF VDRL lacks sensitivity, but a reactive VDRL is diagnostic of neurosyphilis. CSF FTA-ABS lacks specificity, so it should not be routinely performed; a negative FTA-ABS is helpful in ruling out the diagnosis of neurosyphilis.

If a woman was incubating syphilis at the time of delivery, serology can be negative for the mother and infant at the time of birth [8]. Therefore, any infant with findings compatible with syphilis requires investigations irrespective of maternal serological results at delivery.

Which infants need treatment, and with what antibiotics?

Case definitions for congenital syphilis lack consistency because the diagnosis is usually presumptive [7], leading to discrepant recommendations regarding treatment in different scenarios. Table 4 summarizes the recommendations. The treatment of choice is a 10-day course of intravenous crystalline penicillin G of 50,000 units/kg given every 12 h to infants younger than one week of age, every 8 h to infants one to four weeks of age and every 6 h to infants older than four weeks of age [1]. A single dose of long-acting benzathine penicillin G (Bicillin-LA, King Pharmaceuticals, USA) is detectable in the serum of adults for two to four weeks and is likely to be curative of early congenital syphilis in the absence of neurosyphilis. Some experts recommend administration of a single dose or three weekly doses of this product to newborns who have no evidence of congenital syphilis but were born to women adequately treated for syphilis during pregnancy or to women treated for late latent syphilis during or following pregnancy [1][9]. This approach should be discouraged unless follow-up is unlikely to be achieved because the vast majority of these infants are not infected and, in the face of neurosyphilis, this regimen could theoretically result in a temporary decline in infant RPR titres without curing the disease. A common error is the administration of benzyl penicillin G instead of benzathine penicillin. Treatment with non-penicillin antibiotics should be avoided pending efficacy data [1].

Because the suggested treatment regimens do not cure every case of congenital syphilis, follow-up serology is essential and should demonstrate loss of treponemal antibodies by 18 months of age for infants who did not have congenital syphilis or had treatment very early after congenital infection, and a sustained fourfold or greater drop in RPR in all other infants with treated congenital syphilis. A small percentage of cases will require a second course of treatment if RPR titres do not drop as anticipated. If CSF parameters were initially abnormal, CSF should be obtained every six months until normal; the threshold for retreatment should be low if CSF abnormalities persist even at six months of age.

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References

1. Public Health Agency of Canada. Canadian Guidelines on Sexually Transmitted Infections, 2006 edn. Syphilis. www.phac-aspc.gc.ca/std-mts/sti_2006/pdf/510_Syphilis.pdf (Version current at March 27, 2009).
2. Public Health Agency of Canada. Supplement 2004 Canadian sexually transmitted infections surveillance report. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07vol33/33s1/index_e.html (Version current at March 27, 2009).
3. Public Health Agency of Canada. Reported cases of notifiable STI from January 1 to December 31, 2006 and January

1 to December 31, 2007 and corresponding rates for January 1 to December 31, 2006 and 2007.
4. Singh AE, Sutherland K, Lee B, Robinson JL, Wong T. Early congenital syphilis. CMAJ 2007;177:752.
5. Tramont EC. Treponema pallidum (Syphilis). In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's Principles and Practice of Infectious Disease, 6th edn, Volumes 1 and 2. Philadelphia: Elsevier Churchill Livingstone, 2005:2768-85.
6. Harter C, Benirschke K. Fetal syphilis in the first trimester. Am J Obstet Gynecol 1976;124:705-11.
7. Risser WL, Hwang LY. Problems in the current case definitions of congenital syphilis. J Pediatr 1996;129:499-505.
8. Dorfman DH, Glaser JH. Congenital syphilis presenting in infants after the newborn period. N Engl J Med 1990;323:1299-302.
9. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2006. http://www.cdc.gov/std/treatment/2006/rr5511.pd (Version current at March 27, 2009).

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