INESSS
LE SAVOIR PREND FORME

APRIL 2023

PHARMACOLOGICAL TREATMENT

STBBI

SYPHILIS

This optimal use guide is intended mainly for primary care clinicians. It is provided for information purposes only and should not replace the judgment of the clinician who performs activities reserved under an act or regulation. The recommendations concern persons 14 years of age and older[1]. Also, in the case of an infection in a pregnant woman, the follow-up and treatment of the newborn are not covered in this guide. The recommendations were developed using a systematic process and are supported by the scientific literature and the knowledge and experience of Québec clinicians and experts. For further details, go to the section Optimal Usage Guides at inesss.qc.ca.

GENERAL INFORMATION

- Syphilis is an infection caused by the spirochete *Treponema pallidum*, subspecies *pallidum*. It results in a disease with multiple stages, classified as EARLY or LATE syphilis, that can affect different systems.
- The clinical presentation of syphilis is often mistaken for that of other conditions, particularly during the SECONDARY and TERTIARY stages of the disease.
- *T. pallidum* can invade the central nervous system. An untreated infection can resolve spontaneously, remain latent or progress to NEUROSYPHILIS.

Syphilis increases the risk of HIV acquisition and transmission.

Infection during pregnancy can result in adverse fetal or neonatal outcomes (e.g., miscarriage, stillbirth, premature birth, neonatal death or CONGENITAL syphilis).

- The resurgence of syphilis has led to a significant increase in cases in Canada. Men who have sex with men (MSM) are affected more, despite a significant increase in heterosexual populations. The number of cases of congenital syphilis is also on the rise in North America.

Clinical teams need to be vigilant.

TRANSMISSION

- Syphilis is acquired when mucocutaneous syphilitic lesions are present, usually through sexual contact (including oral sex).

CONGENITAL syphilis is caused by vertical transmission during pregnancy.

  - The risk of transmission is directly related to the stage of syphilis during pregnancy and the fetus's length of exposure (risk higher in untreated EARLY syphilis).

- Transmission through blood transfusion or organ donation is documented but rare, due to routine screening.
- Sharing injection equipment is a potential route of transmission.

EARLY syphilis is termed "INFECTIOUS" because it poses the highest risk of contagion, including for the fetus.

SCREENING

Screening should be performed in:

- Any asymptomatic person with risk factors[2];

Any pregnant woman[2] during the first trimester or during the first prenatal vist[3].

  - Screening should be repeated as needed more than once, but at least once around the 28th week of pregnancy and at the time of delivery[3] in the following situations:
    - New exposure;
    - Risk behaviours in a pregnant woman;
    - Risk behaviours or risk factors in any partner.

1. If sexual abuse is suspected, refer to the Guide d'intervention médicosociale pour répondre aux besoins des victimes d'agression sexuelle.
2. Including anyone who requests screening, even if they have not disclosed any risk factors. Consult the Guide québécois de dépistage des ITSS or the tool ITSS à rechercher selon les facteurs de risque décelés.
3. At the time of delivery, if there is no documented serology result, screening serology should be performed.

Québec

CLINICAL PRESENTATION

- EARLY syphilis refers to the PRIMARY, SECONDARY and EARLY LATENT stages of the disease. It covers a period of up to one year after the initial infection.
  - EARLY LATENT syphilis is considered infectious because of the possibility of SECONDARY syphilis symptoms recurring.
- LATE syphilis refers to the LATE LATENT stage (any asymptomatic infection of more than one year's duration) and TERTIARY syphilis.
  - If there is any doubt about the duration of the infection, an asymptomatic person should be considered to have LATENT syphilis of UNKNOWN duration.
- NEUROSYPHILIS can occur at any stage of the disease.
  - Diagnosis is based on a combination of cerebrospinal fluid (CSF) test results (e.g., increased leukocyte count or CSF protein, reactive nontreponemal (VDRL) test result) in the presence of a positive treponemal blood test result and neurological signs and symptoms.

MAIN STAGES OF EARLY SYPHILIS – INFECTIOUS PERIOD — Photos available

Stage	Incubation period	Most common clinical manifestations
PRIMARY syphilis	10 to 90 days (on average, 3 weeks after infection)	• Single chancre at site of inoculation (e.g., genital, anal or oral) • Multiple chancres also possible • Regional adenopathy
SECONDARY syphilis	Usually 2 to 12 or even 24 weeks after infection	• Generalized skin rash • Oral, lingual or genital mucocutaneous lesions (e.g., mucosal plaques) • *Condylomata lata* (hypertrophic lesions resembling flat warts) • Generalized lymphadenopathy • Flu-like syndrome: fever, malaise, headache, muscle pain, joint pain, fatigue • Alopecia • Organ involvement, such as hepatitis (less common) • Neurological manifestations (see NEUROSYPHILIS)
EARLY LATENT syphilis	Infection of less than one year duration	• Asymptomatic • Possible recurrence of SECONDARY syphilis symptoms

MAIN STAGES OF LATE SYPHILIS

Stage	Incubation period	Most common clinical manifestations
LATE LATENT syphilis	Infection of more than one year duration	• Asymptomatic
LATENT syphilis OF UNKNOWN DURATION	Onset of infection cannot be determined	• Asymptomatic
TERTIARY syphilis	5 to 40 years after initial infection	• Cardiovascular syphilis (see APPENDIX 1) • Gummatous syphilis (see APPENDIX 1) • Neurological complications (see NEUROSYPHILIS)

NEUROSYPHILIS

	Incubation period	Most common clinical manifestations
NEUROSYPHILIS	Early manifestations: during the first few months of infection or in the context of SECONDARY syphilis Late manifestations: 10 to 40 years after infection or in the context of TERTIARY syphilis	• Meningitis, meningovascular syphilis • Cranial nerve dysfunction • Otic abnormalities (see APPENDIX 1) • Ocular anomalies (see APPENDIX 1) • General paresis, *tabes dorsalis*

DIAGNOSTIC APPROACH

- The diagnosis of syphilis relies on both the history and clinical presentation and on the serological test results to determine the stage of the infection. The diagnostic approach should include:
  - An assessment of the exposure risk;
  - Checking for a history of syphilis and, if applicable, serological test results and previous treatments;
  - A careful examination of the accessible mucosal surfaces to evaluate for the presence of lesions;
  - A search for signs and symptoms of syphilis if there is a positive serological test result, including:
    - Cardiac auscultation if LATE syphilis is suspected;
    - A search for neurological manifestations, including ocular and otic ones (see APPENDIX 5 for screening questions);
      - If any are found, a specialty consultation is required.

NOTE : The clinical presentation of syphilis is often mistaken for that of other diseases, including HIV. For detailed information on the clinical manifestations and differential diagnoses of syphilis, refer to APPENDIX 1 - MAIN CLINICAL MANIFESTATIONS OF SYPHILIS BY STAGE OF THE INFECTION and APPENDIX 2 - PHOTOS.

LABORATORY TESTS

SEROLOGY

- Serological testing is based on the combination of a treponemal test (TT) and a nontreponemal test (NTT), which are performed sequentially according to one of the detection algorithms: classical (starts with an NTT) or reverse (starts with a TT). A confirmatory test is sometimes necessary. For further information, go to APPENDIX 3 – LABORATORY TESTS - ADDITIONAL INFORMATION.

SIMPLIFIED INTERPRETATION CHART FOR THE SERODIAGNOSIS OF SYPHILIS

Result of serological test			Interprétations possibles
TT	**NTT**	**Confirmatory test (TT)**	
N/A	Nonreactive	N/A	1. No treponematosis (no syphilis) 2. If incubating syphilis is suspected, obtain a 2nd specimen 3 months after the presumed exposure 3. If PRIMARY syphilis is suspected, obtain a 2nd specimen 2 to 4 weeks after symptom onset 4. IF SECONDARY syphilis is suspected, notify the laboratory to assess the possibility of a prozone phenomenon[1] (concerns only the NTT)
Nonreactive	N/A		
N/A	Reactive (all dilutions)	Reactive	1. Syphilitic treponematosis.[2] The clinical presentation and treatment history must be ascertained in order to provide greater certainty in the interpretation: a. EARLY syphilis: PRIMARY, SECONDARY or EARLY LATENT b. LATE LATENT syphilis c. TERTIARY syphilis d. Treated syphilis with persistent reactive RPR
Reactive	Reactive (≥ 1:8)	N/A	
Reactive	Reactive (dilution 1:1 to 1:4)	Reactive or not necessary[3]	
Reactive	Nonreactive	Reactive	1. Syphilitic treponematosis.[2] The clinical presentation and treatment history must be ascertained in order to provide greater certainty in the interpretation: a. PRIMARY syphilis before NTT seroconversion b. SECONDARY syphilis with prozone phenomenon[1] in the NTT c. LATE LATENT syphilis after NTT seroreversion d. Treated syphilis 2. Possible nonsyphilitic treponematosis (bejel, yaws or pinta)
N/A	Reactive (all dilutions)	Nonreactive	1. No treponematosis. NTT and TT falsely negative. 2. If incubating syphilis or PRIMARY syphilis is suspected, obtain a 2nd specimen 2 to 4 weeks later
Reactive	Nonreactive or reactive (dilution 1:1 to 1:4)		

NOTE: This interpretation chart has been simplified. For further information, see the Syphilis detection algorithm

N/A: not applicable (not performed); NTT: nontreponemal test; TT: treponemal test.

1. Prozone phenomenon: a specimen with a high antibody titer may result in a false-negative NTT response when the serum used is not diluted.

2. This disease must be reported by the laboratory and the physician or specialized nurse practitioner.

3. In the presence of a reactive TT whose signal intensity exceeds the cutoff established by the Laboratoire de santé publique du Québec (LSPQ), the confirmatory test is not necessary, even if the NTT titer is low.

LUMBAR PUNCTURE FOR DIAGNOSING NEUROSYPHILIS

✅ **May be considered in the following situations:**	❌ **Not required in the following situations:**
• Presence of clinical signs or symptoms of neurological involvement (see APPENDIX 1) potentially attributable to the infection • TERTIARY syphilis • Inadequate serological response after treatment • Suspected CONGENITAL syphilis	• Ocular or otic abnormalities confirmed on examination, WITH NO cranial nerve dysfunction or other neurological abnormalities.

TREATMENT PRINCIPLES

- **Parenteral penicillin G is the preferred treatment for all stages of syphilis.**

REACTION TO TREATMENT

- A **Jarisch-Herxheimer reaction** may occur within the first few hours after the administration of antibiotic therapy. It usually resolves within 24 hours.
  - Common in EARLY syphilis but can occur at any stage of the infection.
  - It is usually not clinically significant, except in pregnant women or if there is neurological involvement.
  - If it does occur, it manifests as an acute febrile condition with headache, muscle pain, fever, chills, joint pain, sore throat or malaise.
  - This reaction is not an allergy to penicillin.
  - Antipyretics can be used as symptomatic treatment (acetaminophen/NSAIDs).

NEUROSYPHILIS

- A treatment regimen for NEUROSYPHILIS should be used in individuals who have:
  - LATE syphilis with CSF abnormalities;
  - OCULAR syphilis or OTOSYPHILIS, even if the CSF examination is normal or has not been performed

INDIVIDUALS CO-INFECTED WITH HIV

- The treatment of HIV-infected individuals is no different than that of uninfected individuals.

PREGNANT WOMEN

- **Penicillin G is the only antibiotic known to effectively treat fetal infection and prevent CONGENITAL syphilis.**
- **Pregnant women should:**
  - **Receive the penicillin therapy recommended for their stage of infection;**
  - **Be treated as soon as possible to prevent transmission to the fetus:**
    - If there is an anticipated delay before the specialty consultation, initiate treatment before referring the person to a medical specialist;
    - If treatment is administered before the 20th week and there is an adequate serological response, the risk of infection and adverse pregnancy outcomes is minimal.
- **A Jarisch-Herxheimer reaction** can lead to fetal distress and preterm labour.
  - The person should be told that she should seek medical attention if she notices fever, contractions or a decrease in fetal movements within 24 hours after treatment.

ANTIBIOTIC THERAPY

CONSIDERATIONS IF THERE IS A HISTORY OF ALLERGIC REACTION TO PENICILLIN

- **Carefully assess the person's allergy status during the visit (type of involvement, severity, time to onset of symptoms), since an actual allergy will be confirmed in fewer than 10% of adults reporting a history of allergy to penicillin**.
- Confirming the allergy and assessing the possibility of desensitization to penicillin should be considered **prior to the use of an antibiotic other than penicillin G**.

EARLY SYPHILIS: PRIMARY, SECONDARY OR EARLY LATENT (WITH NO NEUROLOGICAL INVOLVEMENT)

FIRST-LINE		OTHER OPTION[1] IF ALLERGY TO PENICILLIN[2]	
Antibiotic and dosage	**Duration**	**Antibiotic and dosage**	**Duration**
Benzathine penicillin G IM (2.4 million units)	A single dose[3]	Doxycycline[4] PO (100 mg) BID	14 days

1. If there is a shortage of benzathine penicillin G or when the first-line treatment is contraindicated. For more information on penicillin G benzathine shortages, including the recommended treatment option during pregnancy consult PHAC's Interim Guidelines.
2. **In case of an allergy to penicillin, especially during pregnancy, desensitization should be considered prior to the use of doxycycline.**
3. In pregnant women, the administration of 2 doses of benzathine penicillin G (one week apart) could be considered, especially during the 3rd trimester, in collaboration with a specialist. See the PHAC syphilis guideline.
4. Doxycycline is not approved by Health Canada for the treatment of syphilis.

LATE SYPHILIS: LATE LATENT, LATENT OF UNKNOWN DURATION OR TERTIARY SYPHILIS (WITH NO NEUROLOGICAL INVOLVEMENT)

FIRST-LINE		OTHER OPTION[1] IF ALLERGY TO PENICILLIN[2]	
Antibiotic and dosage	**Duration**	**Antibiotic and dosage**	**Duration**
Benzathine penicillin G IM (2.4 million units per dose)	Three doses (one per week[3])	Doxycycline[4] PO (100 mg) BID	28 days

1. If there is a shortage of benzathine penicillin G or when the first-line treatment is contraindicated. For more information on penicillin G benzathine shortages, including the recommended treatment option during pregnancy consult PHAC's Interim Guidelines.
2. **In case of an allergy to penicillin, especially during pregnancy, desensitization should be considered prior to the use of doxycycline.**
3. An interval of 7 to 9 days between doses is preferable, although 10 to 14 days may be acceptable in LATE LATENT syphilis, to avoid repeating the entire treatment.
4. Doxycycline is not approved by Health Canada for the treatment of syphilis.

NEUROSYPHILIS, INCLUDING OCULAR AND OTIC MANIFESTATIONS

FIRST-LINE		OTHER OPTION IF ALLERGY TO PENICILLIN[1]	
Antibiotic and dosage	**Duration**	**Antibiotic and dosage**	**Duration**
Aqueous penicillin G IV (18 to 24 million units per day) 3 to 4 million units every 4 hours or continuous infusion	10 to 14 days	Ceftriaxone[1] (2 g per day) IM or IV (limited data)	10 to 14 days

1. **In case of an allergy to penicillin, desensitization should be considered prior to the use of ceftriaxone.** Ceftriaxone is not approved by Health Canada for the treatment of syphilis.

The duration of the penicillin G regimen recommended for NEUROSYPHILIS is shorter than the duration of the regimen used for LATE LATENT syphilis. A single dose of benzathine penicillin G (2.4 million units IM) may be considered after the completion of the intravenous regimen for NEUROSYPHILIS to achieve a comparable total duration of treatment.

FREE MEDICATION

- For individuals registered with the Québec health insurance plan (RAMQ) and who have a valid health insurance card, claim slip or temporary proof of eligibility for medication, enter on the prescription the code **K** (for the infected person) or the code **L** (for partners).

INTERVENTIONS WITH THE INFECTED PERSON

NOTIFIABLE DISEASE

- Syphilis is a reportable disease (MADO), by clinicians, to the regional public health department. To do this, complete the notifiable disease/infection/intoxication (MADO) notification form in accordance with the *Public Health Act* AS 770.
  - Inform the infected person that syphilis is a reportable disease to the public health department and that they, the person, may be contacted for an epidemiological investigation.

MANAGEMENT

- In addition to a medical and sexual history, diagnosis, treatment and appropriate FOLLOW-UP management should include the following:
  - Encouraging or providing other preventive measures;
  - Counseling on the importance of partner notification;
  - Education and advice on the infection (transmission, prevention and complications) and risk reduction:
    - Advise individuals with EARLY syphilis to abstain from all sexual relations for up to one week after a single dose of IM benzathine penicillin G treatment, after 7 days of IV aqueous penicillin G or until completion of a course of doxycyclin or IV ceftriaxone, AND until the symptoms resolve if they have potentially infectious lesions;
    - **Stress the importance of the follow-up and of repeating the serological tests** to monitor the response to treatment:
      - Inform the person that they may continue to have a positive treponemal test result for life, even after effective treatment, and that the NTT titer may remain reactive for a prolonged period.
    - Inform the person of safer sexual practices and of the importance of consistently using barrier protection.
- The regional public health department can support the clinical team for preventive intervention with individuals with an STBBI and their partners.
- For additional management-related resources, see APPENDIX 4 – ADDITIONNAL INFORMATION AND RESOURCES

CONSIDERATIONS REGARDING HIV

- In the presence of a reactive serology for syphilis, **HIV screening should be performed**.
  - **Pre-exposure prophylaxis (PrEP) should be discussed** with individuals at risk for contracting HIV.

MANAGEMENT OF PREGNANT WOMEN

A specialty consultation is required.

- An ultrasound evaluation of the fetus should be performed to check for CONGENITAL syphilis (see the section Pregnant women and congenital syphilis).
- Prior to birth, a plan for managing the newborn should be prepared in collaboration with the team of professionals involved in the delivery and neonatal follow-up.

INTERVENTIONS WITH THE PARTNERS

MANAGEMENT

- Management requires a **clinical and serological evaluation**. Empirical treatment is sometimes required.
  - Sexual partners should include everyone who has had oral, genital or anal sex with a person who has probable or confirmed EARLY syphilis, **whether barrier protection was used or not**.
  - To identify the partners to be confidentially informed of the exposure and the need for an evaluation, see APPENDIX 4 – IDENTIFICATION OF PARTNERS TO BE NOTIFIED or the tool Soutenir la personne atteinte d'une ITSS pour qu'elle avise ses partenaires : quatre étapes.
- The partner(s) of an individual with EARLY syphilis should abstain from all sexual activity for 7 days after receiving empirical treatment or until their syphilis serology shows that they were not infected.

TREATMENT OF PARTNERS

- **Immediate empirical treatment** (presumptive treatment for EARLY syphilis) should be offered to persons who have had sex with:
  - An individual with EARLY syphilis or syphilis of UNKNOWN DURATION during the 90 days preceding diagnosis, especially if a follow-up of those partners cannot be provided, **regardless of the serology result obtained**;
  - An individual with EARLY syphilis or syphilis of UNKNOWN DURATION more than 90 days preceding diagnosis **if the serology test results of those partners are not available or if the possibility of a follow-up with them is uncertain**.
- Long-term sexual partners of individuals with LATE LATENT syphilis should be evaluated clinically and serologically for syphilis and treated according to the results of the evaluation.
- Screened partners with positive laboratory test results should be treated.

FOLLOW-UP

POST-TREATMENT CLINICAL AND SEROLOGICAL FOLLOW-UP

- **A clinical and serological follow-up (changes in NTT titer) must be provided** to determine the response to treatment and to permit a more accurate interpretation of the subsequent NTTs.
- Titers should be monitored until they become negative or low and stable (e.g., ≤ 1:4).
- Definitive criteria for assessing cure or treatment failure have not been clearly established. A 4-fold decline in the post-treatment NTT titer (see table below) generally indicates an adequate response.
- Some adequately treated individuals may become **serofast**, which is characterized by a low and persistent NTT titer (≤ 1:4). Annual serological screening could facilitate their follow-up, especially if they are in at-risk groups.

STAGE / POPULATION	FREQUENCY OF LABORATORY TESTS	EXPECTED RESPONSE AFTER TREATMENT
EARLY syphilis and LATENT SYPHILIS OF UNKNOWN DURATION	• 3, 6 and 12 months after treatment	• 4-fold decline in the NTT titer in a period of 6 to 12 months
LATE LATENT or TERTIARY syphilis	• 12 and 24 months after treatment	• 4-fold decline in the NTT titer in a period of 12 to 24 months
NEUROSYPHILIS (including OCULAR syphilis and OTOSYPHILIS)	• Serology: 6, 12 and 24 months after treatment • CSF: There is no need to repeat CSF testing if there is an adequate serological and clinical response.	• Normalization of the serum NTT titer (according to the stage at which the neurological manifestations occurred) is predictive of the normalization of the CSF parameters.
Pregnant women and CONGENITAL syphilis	**Early follow-up is necessary to ensure a good therapeutic response** • Monthly (starting from the last dose of treatment) until the NTT titer is 1:8 or less, then quarterly and • At delivery • Then at 12 months (and at 24 months in the case of TERTIARY SYPHILIS)	• 4-fold decline in the NTT titer before birth (if not achieved, it does not necessarily mean treatment failure) or • Achievement of an NTT titer ≤ 1:8

NOTE : A 4-fold decline in the NTT titer represents a decrease of 2 dilutions (e.g., from 1:32 to 1:8). The dilutions proceed as follows: Non reactive, 1:1, 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, 1:256, etc.

REINFECTION

- Reinfection is usually diagnosed by an increase of at least 2 dilutions (4-fold increase in the titer) for an NTT.
  - Retreatment should be administered according to the stage determined.
  - Reinfection may be difficult to distinguish from treatment failure.

TREATMENT FAILURE

- The possibility of a relapse or treatment failure should be considered in a person with an inadequate serological response following treatment for syphilis.
  - A clinical follow-up should be provided and include screening for neurological manifestations.
  - If there are no neurological manifestations, a lumbar puncture may be considered, on the advice of a specialist.
  - Retreatment should be administered as for LATE LATENT syphilis or NEUROSYPHILIS, as the case may be.

CONSULTATION WITH A MEDICAL SPECIALIST OR AN EXPERIENCED COLLEAGUE

- The infected person should be jointly managed or referred to a specialist in the following situations:
  - Suspected NEUROSYPHILIS, OCULAR SYPHILIS or OTOSYPHILIS
  - Specific organ involvement (e.g., cardiovascular syphilis, gummatous syphilis)
  - Reported history of allergy or contraindication to penicillin
  - Treatment failure
  - Management of pregnant women
- Call on a specialist or experienced colleague, if necessary:
  - If reinfection is suspected
  - For the interpretation of serology results, which can be complex
  - When considering the use of an alternative treatment

REFERENCES

To consult the references, see the report accompanying this optimal use guide.

MAIN CLINICAL MANIFESTATIONS OF SYPHILIS BY STAGE OF THE INFECTION

	Clinical manifestations	Symptoms, signs and presentation (list not exhaustive)	Natural course without treatment	Possible differential diagnoses (list not exhaustive)
PRIMARY syphilis	Chancre	• Papule that progresses to an ulcer that is classically single, painless, indurated and superficial, with a regular contour and localized at the site of inoculation (e.g., in the genital, anal or oral area). • Chancres may also be multiple, atypical or painful.	• Spontaneous regression in 3 to 6 weeks	• Herpes • Lymphogranuloma venereum • Mpox • Chancroid
	General systemic symptoms	• Regional adenopathy		
SECONDARY syphilis	Cutaneous involvement	• Generalized skin rash, often maculopapular, on the trunk. The rash regularly reaches the palms and soles of the feet. • Oral, lingual or genital mucocutaneous lesions (e.g., mucous patches). • *Condylomata lata*, hypertrophic lesions resembling flat warts in warm, moist areas.	• Spontaneous regression in 3 to 12 weeks • Then goes into latency • Symptoms may recur for about a year	• Mononucleosis syndrome or other viral exanthem • Primary HIV infection • Drug-induced rash • Pityriasis rosae • Guttate psoriasis
	General systemic symptoms	• Generalized lymphadenopathy • Flu-like syndrome: fever, malaise, headache, muscle pain, joint pain, fatigue		
	Organ involvement	• Hepatitis		
	Alopecia	Spotty, patchy, sparse or diffuse alopecia		
	Neurological manifestations	See NEUROSYPHILIS		

MAIN CLINICAL MANIFESTATIONS OF SYPHILIS BY STAGE OF THE INFECTION

	Clinical manifestations	Symptoms, signs and presentation (list not exhaustive)
TERTIARY syphilis	Cardiovascular syphilis	• Aortic aneurysm • Aortic insufficiency • Coronary artery ostial stenosis
	Gummatous syphilis	• Nodules/plaques or ulcers affecting skin, mucosae, visceral organs, or bones
	Neurological complications	• See NEUROSYPHILIS

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MAIN CLINICAL MANIFESTATIONS OF SYPHILIS BY STAGE OF THE INFECTION

<table>
<tr><th></th><th>Clinical manifestations</th><th colspan="2">Symptoms, signs and presentation (list not exhaustive)</th></tr>
<tr><td rowspan="5">NEUROSYPHILIS</td><td>Early manifestations</td><td colspan="2">• Meningitis†
- Headache, neck stiffness, fever, photophobia, nausea, vomiting, confusion
- Cranial nerve dysfunction (cranial neuritis)
- Epileptic seizures
• Meningovascular syphilis† (stroke)
- Hemiparesis, hemihypoesthesia, dysphasia, hemianopsia
- Epileptic seizures
• Otic abnormalities (see OTOSYPHILIS)
• Ocular abnormalities (see OCULAR syphilis)
• Papillar oedema</td></tr>
<tr><td>Late manifestations</td><td colspan="2">• Parenchymatous neurosyphilis
- General paresis
• Progressive cognitive impairment
• Personality changes
• Psychiatric disorders (e.g., psychosis)
- Tabes dorsalis
• Sensory ataxia (ataxia, impaired pallesthesia, impaired proprioception, areflexia)
• Paroxysmal pain in the limbs, back and face
• Incontinence
• Argyll Robertson pupils are often a feature
• Otic abnormalities (see OTOSYPHILIS)
• Ocular abnormalities (see OCULAR syphilis)</td></tr>
<tr><td rowspan="2">OCULAR syphilis</td><td>Symptoms and signs</td><td>Diagnoses (e.g., after a slit lamp examination)</td></tr>
<tr><td>• Blurred vision
• Redness of the eye
• Visual loss
• Flashing lights
• Floaters</td><td>• Uveitis
• Optic neuritis
• Other neuro-ophthalmological manifestations
• Keratitis
• Conjunctivitis</td></tr>
<tr><td>OTOSYPHILIS</td><td colspan="2">• Hearing loss, tinnitus, vertigo</td></tr>
</table>

† Although meningitis and meningovascular syphilis usually occur early, they can also occur late.

MAIN CLINICAL MANIFESTATIONS - SPECIAL POPULATIONS

	Clinical manifestations	Symptoms, signs and presentation (list not exhaustive)
HIV co-infection	More aggressive and atypical signs of infection or more rapid progression to NEUROSYPHILIS are possible but rarely observed in individuals on antiretroviral therapy, who are not immunocompromised.	
Pregnant women	Ultrasound signs of CONGENITAL syphilis	• Usually observed after 18 to 20 weeks of gestation • Include intrauterine growth restriction, hepatomegaly, splenomegaly, fetal anemia, polyhydramnios, placentomegaly, *hydrops fetalis*, ascites, pericardial effusion, bone abnormalities and fetal death

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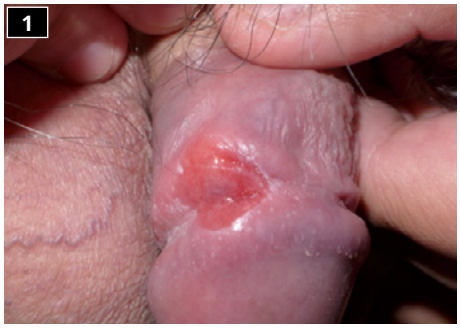
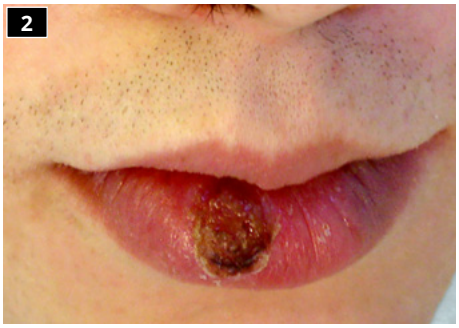
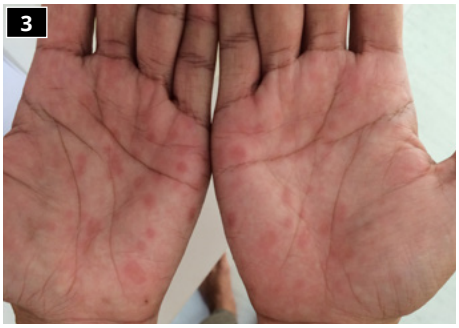
SYPHILIS – DIAGNOSTIC AID



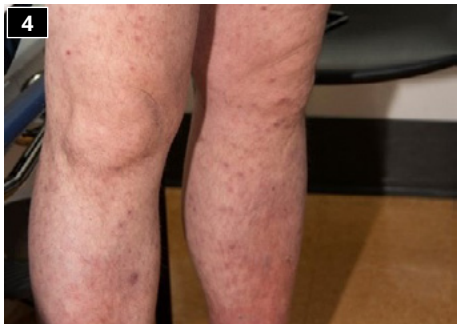
1. PRIMARY syphilis, genital chancre



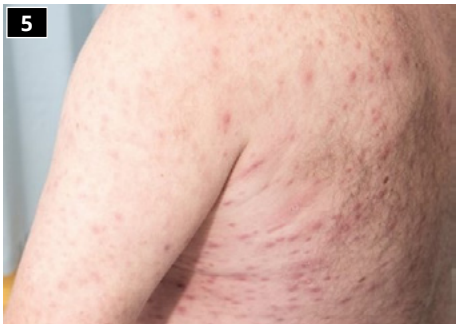
2. PRIMARY syphilis, chancre on the lip



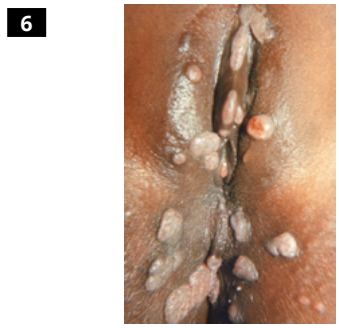
3. SECONDARY syphilis, palms involvement



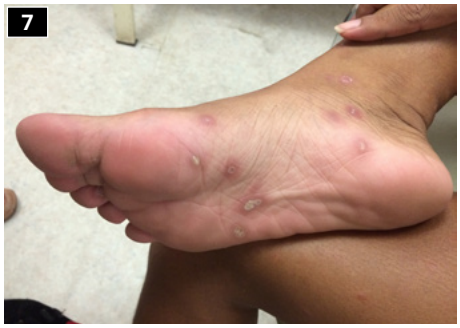
4. SECONDARY syphilis, rash on the legs



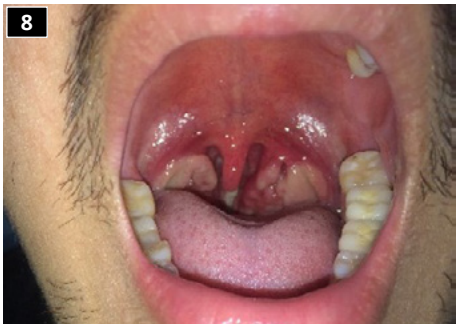
5. SECONDARY syphilis, rash on the trunk



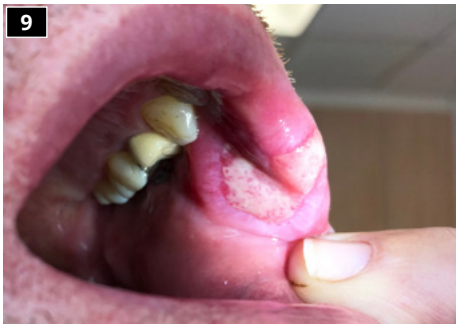
6. SECONDARY syphilis, condylomta lata on genital and perianal regions



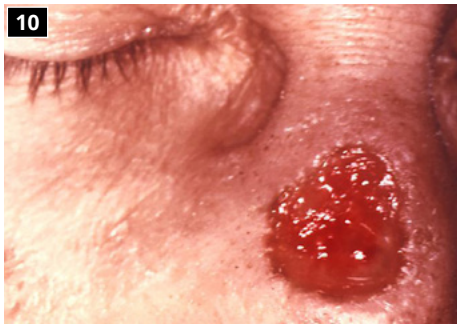
7. SECONDARY syphilis, soles involvement



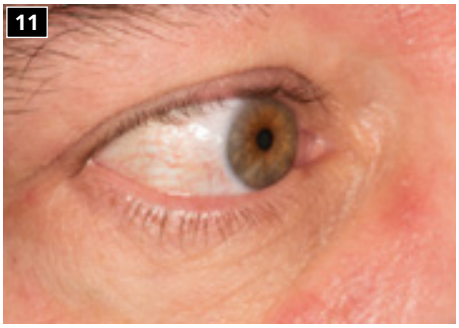
8. SECONDARY syphilis, mucous pathches



9. SECONDARY syphilis, mucosal involvement



10. TERTIARY syphilis, cutaneous ulcerative lesion on the nose



11. OCULAR syphilis, redness of the conjunctive

Source:

All the photos in this tool were reproduced with their author's permission. For further details regarding the source of these photos, consult the additional appendices to the report in support of the syphilis optimal use guide.

Return to CLINICAL PRESENTATION

LABORATORY TESTS - ADDITIONAL INFORMATION

DIRECT DETECTION TESTS

- Darkfield microscopy is no longer available in Québec.
- Although the diagnosis of syphilis chancre is primarily clinical, in certain situations (e.g., negative serology at initial presentation because of the window period, atypical lesion), a nucleic acid amplification test (NAAT) might be considered in collaboration with a specialist or an experienced colleague. If congenital syphilis is suspected, a NAAT may also be used on the placenta at the multidisciplinary team's discretion. The specimens to be analyzed by NAAT will be forwarded to the LSPQ by the laboratory team.

SEROLOGY

TYPES OF TESTS USED IN QUÉBEC

Test	Used mainly for:	Tests performed in the system's laboratories	Details
TREPONEMAL TEST (TT)	• Initial screening or diagnostic purposes (in laboratories that use the reverse algorithm)	• Enzyme Immunoassay (EIA) • Chemiluminescence immunoassay (CIA)	• Remains positive for life, although seroreversion can occur in some individuals
	• Confirmation (performed at the LSPQ)	• *T. pallidum* particle agglutination test (TP-PA) • Line Immunoassay (INNO-LIA)	
NONTREPONEMAL TEST (NTT)	• Initial screening or diagnostic purposes (in laboratories that use the classical algorithm) • Additional test when the TT is reactive (in laboratories that use the reverse algorithm) • Help precise the stage of infection • Follow-up (response to treatment) • Detection of reinfection	• Test on serum: rapid plasma reagin (RPR) test • Test on CSF: Venereal Disease Research Laboratory (VDRL) test	• Qualitative or quantitative • Titer correlates with disease activity

Procedure if known history of syphilitic infection

- Only the NTT will be performed qualitatively and, if reactive, quantitatively in the following situations:
  - Documented confirmatory test in the past;
  - Positive TT in the past and previous reactive NTT result confirming the infection with no further testing (usually > 1:4).

Serology results can vary

- The quantitative results of nontreponemal tests can vary for a given individual when specimens are analyzed by different laboratories or using different assays.

Serology results can be falsely negative

- The prozone effect is an *in vitro* phenomenon that occurs in NTTs whereby a specimen with a high antibody titer result in a false-negative response when the serum used is not diluted.
- TT and NTT results can be falsely negative during the window period (up to 3 months).
- The NTT can also be nonreactive in LATE syphilis.

Serology results can be falsely positive

- The possible causes of a false-positive result (TT or NTT) include various medical conditions, such as:
  - Acute febrile illnesses;
  - Autoimmune disorders;
  - Vaccinations;
  - Pregnancy;
  - Injection drug use;
  - Intravenous immunoglobulin administration;
  - Other infections (e.g., nonsyphilitic treponematoses, leptospirosis)

Additional information

- For further details on serological testing, see the materials produced by the Institut national de santé publique du Québec:
  - Algorithme de détection de la syphilis
  - Confirmation de la présence d'anticorps contre la syphilis (Guide des services)
  - Détection de la neurosyphilis (Guide des services)

Return to LABORATORY TESTS

IDENTIFICATION OF THE PARTNERS TO BE NOTIFIED

STAGE OF SYPHILIS	SEXUAL CONTACT WITH THE INFECTED INDIVIDUAL (taken from the MSSS's recommendations)
PRIMARY	• 3 months before symptom onset • Date of symptom onset not known: 4 months and one week before specimen is obtained
SECONDARY	• 6 months before symptom onset • Date of symptom onset not known: 8 months before specimen is obtained
EARLY LATENT	• 12 months before specimen is obtained
LATE LATENT	• NTT titer ≤ 1:32 → Current or former partners who had or have had a long-term relationship with the infected individual • NTT titer > 1:32 → Partners in the past year

ADDITIONAL INFORMATION AND RESOURCES

NOTIFIABLE DISEASE (MADO)

- The information to be provided for syphilis cases includes:
  - Information about donating and receiving blood, blood products, tissues or organs;
  - Information about the stage of the disease.
- For information about mandatory notification, go to the MSSS's website or consult the Guide québécois de dépistage des ITSS.

MANAGEMENT OF SPECIAL POPULATIONS

For additional resources on the management of pregnant women and on CONGENITAL SYPHILIS, consult the following:

- The Canadian Paediatric Society article Congenital syphilis: No longer just of historical interest
- The following MSSS and Collège des médecins du Québec (CMQ) publications: Appel à la vigilance and Syphilis et grossesse : redoubler de vigilance!

STBBI PREVENTION INTERVENTIONS

During a medical visit, for instance, about an STBBI or contraception or for routine clinical examination, the clinical team should:

- Inquire about STBBI risk factors and screen accordingly, as many people are asymptomatic and do not know that they are infected:
  - ITSS à rechercher selon les facteurs de risque décelés
  - Estimation du risque associé aux activités sexuelles
- Vaccinate in accordance with the current standards:
  - Protocole d'immunisation du Québec
  - Vaccination et ITSS
- As needed, consult the various MSSS tools concerning STBBI preventive interventions, such as the following:
  - Guide de la PPrE pour les professionnels de la santé du Québec
  - Soutenir la personne atteinte d'une ITSS pour qu'elle avise ses partenaires : quatre étapes
  - Outils de prévention clinique des ITSS
  - Prélèvements et analyses recommandés chez une personne asymptomatique - Syphilis, hépatites B et C, VIH
  - Personne exposée à une ITSS : que faire?
  - Recrudescence de la lymphogranulomatose vénérienne au Québec : détection et traitement
  - Ressources – Intervention préventive relative aux ITSS
  - Site Internet, dépliants et brochures à l'intention des patients (p. ex. Entre caresses et baisers, une ITSS s'est faufilée… Il faut en parler)

PUBLIC HEALTH AGENCY OF CANADA (PHAC) PUBLICATIONS

- Sexually transmitted and blood-borne infections: Guides for health professionals
- Interim Syphilis Treatment Guidelines during the Benzathine Penicillin G (Bicillin L-A) Shortage
- Syphilis in Canada: Technical report on epidemiological trends, determinants and interventions

INESSS PUBLICATIONS

- Optimal usage guides for pharmacological treatment of sexually transmitted and blood-borne infections (STBBI)
- Confirmed Mycoplasma genitalium Infection

Return to INTERVENTIONS WITH THE INFECTED PERSON

SCREENING QUESTIONS FOR NEUROSYPHILIS (INCLUDING OCULAR SYPHILIS AND OTOSYPHILIS)

Symptoms of OTOSYPHILIS
1) Have you recently had new trouble hearing? 2) Do you have ringing in your ears?
Symptoms of OCULAR syphilis
3) Have you recently had a change in vision? 4) Do you see flashing lights? 5) Do you see spots that move or float by in your vision? 6) Have you had any blurring of your vision?
Symptoms of NEUROSYPHILIS
7) Are you having headaches? 8) Have you recently been confused? 9) Has your memory recently gotten worse? 10) Do you have trouble concentrating? 11) Do you feel that your personality has recently changed? 12) Are you having a new problem walking? 13) Do you have weakness or numbness in your legs?
⚠ **All of these symptoms are nonspecific. If isolated, they do not necessarily warrant a neurology consultation, which should be requested based on clinical judgment.** Health professionals should consider evaluation and treatment for neurosyphilis in individuals with new persistent headaches rated as moderate or greater; new change in vision, including loss, blurring, or seeing spots or flashing lights; new change in hearing, including loss, muffling or tinnitus; new and persistent change in personality, memory or judgment; new numbness in both legs; or new gait incoordination.

Screening Questions for Neurosyphilis (Including Ocular and Otosyphilis)

Source: Public Health Seattle and King County, January 21, 2015.

Return to DIAGNOSTIC APPROACH