Syphilis:
Stemming the Outbreak

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The diagnosis of syphilis may be difficult as, shortly after infection, serum investigations may not be positive. In the later stages, additional investigations, specifically cerebrospinal fluid analysis, may be necessary. The clinical manifestations of syphilis are varied and can mimic countless other conditions (Table 1).[1]

Spread by direct contact with spirochetes, which are abundant in the lesions of primary or secondary syphilis, the disease is transmitted through sexual contact or by merely touching the lesion. Congenital syphilis occurs by the passage of *Treponema pallidum* through the placenta. There have also been reports of syphilis being spread through transfused blood and blood products.

Syphilis should always be suspected in a person who presents with lesions compatible with the disease, as infection with *T. pallidum* does not confer lifelong immunity, even if previously treated.

What are the stages of syphilis?

Syphilis progresses through a seemingly ordered series of steps:

Primary syphilis

After a nine- to 90-day incubation period, primary syphilis presents as a painless, indurated chancre at the site of inoculation with *T. pallidum*. Depending on its location, it may go undetected. This phase is associated with an early bacteremia. A secondary bacteremia ensues, resulting in the widespread dissemination of the spirochete, leading to a characteristic mucocutaneous manifestation of secondary syphilis.

Natalie's Presentation

Natalie, 36, presents with a painless ulceration, which has been present on the right labia majora for approximately one month (Figure 1). She thinks it is improving, but it has been associated with right inguinal lymphadenopathy and she is concerned it may be cancer.

Natalie's medical history is remarkable for multiple sexual partners, the most recent of which was approximately eight weeks prior to the onset of the lesion. She engaged in unprotected intercourse and recalls that her partner had a small lesion on his penis.

A scraping from the base of the lesion was submitted for dark field microscopy, which did not reveal any obvious pathogens. A serum sample was obtained for venereal diseases research laboratory (VDRL) analysis. In addition, serology was obtained for hepatitis B and C and HIV. Endocervical swabs were obtained for detection of *Chlamydia trachomatis* and *Neisseria gonorrhea*. Presumptive therapy was administered for primary syphilis (1.2 million units of benzathine penicillin G into each buttock), chlamydia (azithromycin, 1 g single dose), and gonorrhea (ceftriaxone, 125 mg, intramuscularly).

Three days later, the VDRL result revealed a titer of 1:64 dilutions, supportive of a diagnosis of syphilis. Over the next year, the VDRL titer became 1:8 dilutions, indicating an adequate response to therapy. All other laboratory investigations were negative.

Figure 1. A close up of Natalie's vulvar ulcer at time of presentation.

Secondary syphilis

Secondary syphilis presents with non-puritic, maculopapular eruptions that extend from head to toe, including the palms and soles.

Table 1

Syphilis: Clinical manifestations and differential diagnosis according to stage

Stage	Incubation period	Clinical manifestations	Differential diagnosis
Primary syphilis	• 9-90 days after exposure • Resolves spontaneously within 3-6 weeks	**Chancre**: Solitary, painless ulcer with indurated edges	• Genital herpes • Chancroid • Ectoparasite infection • Trauma • Neoplasm • Autoimmune disease: Behect's syndrome, Crohn's disease, Reiter syndrome
Secondary syphilis	• 6 weeks–6 months after exposure • Resolves spontaneously in a variable period of time; most patients enter the latency stage withinthe first year of infection	**Skin and mucous membranes:** Alopecia, papulosquamous eruption, condylomata lata **Constitutional Symptoms**: Fever, malaise, lymphadenopathy, arthralgia **Renal:** Glomerulonephritis, neprhotic syndrome **Hepatic:** Hepatitis **Central Nervous System:** Headache, meningismus, cranial neuropathy, iritis, uvetis cranial nerve palsies **Muskuloskeletal:** Arthalgias, periostitis	• Primary infection with HIV • HIV reconstitution syndrome • Pityriasis rosacea • Psoriasis • Erythema multiforme • Tinia versicolor • Lichen • Drug eruption • Viral exanthem • Ectoparasite infection
Latent syphilis	• Progresses directly from untreated secondary syphilis • Early latent syphilis: duration < 1 year • Late latent syphilis: duration > 1 year.	None	None
Tertiary syphilis	• 10–30 years after exposure	**Gummatous disease:** Granulomas, irregularly shaped cutaneous plaques or nodules which may ulcerate to deeper subcutaneous structures. Gummas may cause perforation of the pallet, destruction of nasal cartilage leading to saddle-nose deformity, and may mimic neoplasms	• Tuberculosis • Sarcoidosis • Neoplasm • Deep fungal infections
		Cardiovascular disease: Aortitis, which may be asymptomatic or associated with dilation of the ascending aorta with aneurysm formation and aortic insufficiency	• Aneurysms • Ischemic heart disease
		Neurosyphilis: Seizures, ataxia, aphasia, paresis, hyperreflexia, personality changes, cognitive impairment, visual changes (pupilary abnormalities; optic atrophy), cranial nerve paresis, peripheral neuropathy, altered bowel and bladder function, hearing loss, "lightning pains" in lower extremity	• Multiple sclerosis • Psychiatric conditions • Cerebral vascular accidents • Dementia

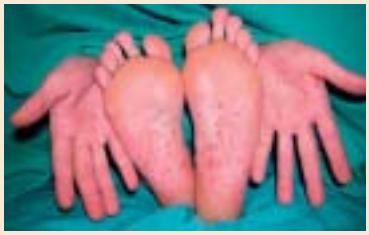
John's Case

John, 45, presented to his family physician with a five-week history of a papulosquamous eruption covering his entire body. He denied allergies or other significant medical problem. His last sexual contact was approximately four months prior, at which time he had unprotected intercourse with three different women in the same month. Approximately two months after his sexual encounters, he recalls developing an ulceration on his penis. It was painless, persisted for approximately one month, and resolved spontaneously. Shortly thereafter, he developed an eruption (Figures 1, 2).

John's VDRL titer was 1:512 dilutions and serology for HIV and hepatitis B and C were negative, as was a urine specimen for identification of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. A diagnosis of secondary syphilis was established based on the positive VDRL and papulosquamous eruption.

The patient received intramuscular benzathine penicillin G, 1.2 million units administered into each buttock (2.4 million units total). Azithromycin, 1 g, orally, and ceftriaxone, 125 mg, intramuscularly were also administered for presumptive management of chlamydia and gonorrhea, respectively.

Over the next year, the VDRL titer became 1:8 dilutions, suggesting successful treatment. The papulosquamous eruption resolved, however, he has been left penny sized hyperpigmented scars on the backs of the calves at the sites of the leg lesions.



Figures 1, 2. Head to toe maculopapular eruptions.

Condyloma lata, another secondary form of syphilis, may be confused with condyloma acuminata (genital warts). The lesions of condyloma lata are usually moist, grey-white to erythematous, plaque-like, and appear approximately six months after infection. These lesions are highly infectious and appear surrounding the genitalia, anus, axillae, and beneath the breasts. In the mucous membranes of the mouth and vagina, these lesions may appear as flat hyperkeratotic areas.

Constitutional symptoms are common in secondary syphilis, specifically fatigue, low-grade fever, malaise, weight loss, and generalized lymphadenopathy. The central nervous system may also be involved during the spirochetemia, manifesting with headache, visual disturbances, and cranial nerve abnormalities. Since the spirochetes can invade all organs, other manifestations such as hepatitis, alopecia, synovitis, osteitits, periostitis, and renal abnormalities may occur.

Latent syphilis

If untreated, secondary syphilis may progress to a period of subclinical infection, or a latent stage (early latent, ≤ 1 year duration; late latent, > 1 year duration). This stage is asymptomatic and can only be detected with a serum laboratory investigation.

Tertiary syphilis

Tertiary syphilis, which has an incubation period of 10 to 30 years, has protean manifestations. Meningovascular disease or other significant neurologic manifestations, such as general paresis or tabes dorsalis, may occur in tertiary syphilis.

In addition to neurosyphylis, other non-infectious manifestations of tertiary syphilis can include cardiovascular and gummatous syphilis.

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How is syphilis diagnosed?

Table 2 outlines laboratory investigations used to diagnose syphilis. A high index of suspicion is necessary when evaluating patients presenting with genital ulcers and skin eruptions.

The most well-established technique for investigating active cutaneous lesions is dark field microscopy, which entails obtaining serous exudate from the base of the ulcerations or mucous membrane lesions and directly examining the specimen under a dark field. Observation of the corkscrew-shaped spirochete establishes the diagnosis. Caution must be exercised if the lesion is located in the mouth, as oral spirochetes may represent a false positive.

Patients suspected of having syphilis are initially evaluated with a non-treponemal serologic test, such as a rapid plasma reagin (RPR) or venereal diseases research laboratory (VDRL) test to detect the production of non-specific antibodies that react with cardiolipin.

A number of conditions can lead to false positive non-treponemal tests. Because RPR is a screen, if testing is performed too soon after infection (it takes two to 12 weeks to become positive), a false negative result may occur. Therefore, high-risk individuals, or known contacts of an infectious syphilis case, should be provided with confirmatory and reference testing. As the titer will gradually decrease over time, non-treponemal tests—which are inexpensive, reliable, and easy to perform—may be used to monitor response to treatment.

If a non-treponemal test is positive, a confirmatory test, such as the *T. pallidum* hemagglutination (TPHA) test, or the fluorescent treponemal antibodies—absorption test (FTA-abs) test, is performed. Unlike the non-treponemal tests that will decline in titer or become non-reactive with effective treatment, these tests will remain positive for life. Therefore, the treponemal-specific tests are effective for confirming infection, but are not useful for monitoring efficacy of treatment.[2]

Early in the infection, the VDRL and FTA-abs may both be negative, as the patient has not had sufficient time to mount an adequate immune response. However, by late primary or secondary syphilis, these tests should be positive.

People engaging in unprotected sex, especially with anonymous sex partners, anyone with a sexually transmitted disease, genital ulcer disease, pregnant women, or those immigrating to Canada should be tested for syphilis.

When is a lumbar puncture necessary?

Treponema pallidum invades the central nervous system early in the infection, therefore, people with a persistent central nervous system infection are at high risk for neurosyphilis. The diagnosis of asymptomatic neurosyphilis can be established by detecting a pleocytosis, elevated total protein concentration, depressed glucose concentration, and a reactive VDRL in the cerebrospinal fluid.

Criteria for performing a lumbar puncture in those with syphilis were designed to detect people at the highest risk for neurosyphilis. They include:

- people with neurologic or opthamalogic complaints,
- people with late latent syphilis or syphilis of unknown duration in a patinet with HIV infection,
- people with active tertiary syphilis, or
- treatment failure in non-neurologic syphilis.

When a lumbar puncture is performed, the cerebrospinal fluid should be submitted for protein analysis, cell count, glucose levels, and VDRL.

Table 2

Diagnosis and treatment of syphilis according to stage

Stage	Diagnosis (Sensitivity)	Treatment
Primary	• Dark-field microscopy of exudates from base of lesion (80%) • Non-treponemal tests–VDRL(78-86%) • Treponomal–specific tests (76-84%)	• Benzathine penicillin G, 2.4 million units IM, single dose, (1.2 million units into each buttock) *Alternatives:* *Penicillin allergic, non-pregnant* • Doxycycline, 100 mg, po bid for 2 weeks • Ceftriaxone, 1 g, od IM or IV for 8-10 days *Penicillin allergic, pregnant* • Penicillin desensitization and benzathine penicillin G, 2.4 million units IM • Azithromycin, 2 g, po single dose
Secondary	• Dark-field microscopy of skin lesion (80%) • Non-treponemal tests (100%) • Treponomal–specific tests (100%)	Same as primary syphilis
Latent • Early latent Syphilis (< 1 year duration) • Late latent (> 1 year duration	• Non-treponemal tests (95-100%) • Treponemal-specific tests (97-100%)	• Early latent syphilis: Same as for primary and secondary syphilis • Latent syphilis: Benzathine penicillin G, 2.4 million units, IM (1.2 million units into each buttock) once weekly for 3 weeks *Penicillin allergic:* • Doxycycline, 100 mg, po bid for 4 weeks
Tertiary	• Non-treponemal tests (71-73%) • Treponemal–specific tests (94-96%) • Cerebrospinal fluid examination	Aqueous crystalline penicillin G, 3-4 million units, IV every 4 hours for 10-14 days or procaine penicillin G, 2.4 million units, IM daily, and probenicid, 500 mg, po qid for 10-14 days Penicillin-allergic patients: No proven effective alternatives; desensitization should occur; for administration of penicillin
Congenital • Early: < 1 year • Late: > 1 year	• Obtain venous blood specimens for serology on child and mother: non-treponemal and treponemal specific test • Placenta examined by dark field examination • If skin lesions or rhinitis present, obtain specimens for dark field microscopy	• Crystalline penicillin G, 50,000 U/kg, IV every 12 hours for the first week of life; 8 hourly thereafter, for 10 days total therapy. *Abnormal cerebrospinal fluid or neurologic involvement*: • Crystalline penicillin G 200,000 U/kg/day, IV every 6 hours for 10-14 days *Normal cerebrospinal fluid and no neurologic involvement*: • Crystalline penicillin G, 200,000 U/kg/day, IV every 6 hours for 10-14 days or benzathine penicillin G, 500,000 U/kg, IM (maximum 2.4 million units) weekly for 3 weeks

VDRL: Venereal diseases research laboratory
IM: Intramuscular
IV: Intravenous
po: Orally
bid: Twice a day
qid: Four times daily

What is congenital syphilis?

Congenital syphilis occurs when there is *in utero* infection of the fetus in an untreated, or inadequately treated mother. Although it can occur at any stage, it is more likely to occur during the early stages of syphilis. Depending upon the severity of the infection, late abortion, stillbirth, neonatal death, and neonatal disease or latent infection can occur.[2]

The differential diagnosis of neonatal congenital syphilis includes other generalized congenital

Table 3

Public health interventions for persons diagnosed with syphilis

1. Syphilis is a reportable sexually transmitted infection in all provinces and territories. Report to the public health department immediately.
2. Ensure prompt treatment of current case according to recommended treatment guidelines.
3. Evaluation of current case for risk factors and testing of other sexually transmitted infections:
   - Chlamydia, gonorrhea (epidemiologic treatment if required)
   - Hepatitis B, offer Hepatitis B vaccination if suspected
   - HIV
4. Contact tracing/Partner notification

Rapid identification and investigation of sexual partners is essential to locate persons with early syphilis and provide them with treatment to prevent further transmission:

- Interview the case to identify potential additional cases in persons who may be at risk of contracting the infection
- All sexual partners of index case within the following period must be located and appropriately evaluated:
  - Primary syphilis: 3 months before development of symptoms
  - Secondary syphilis: 6 months before development of symptoms
  - Latent syphilis:
    - Early latent: For 1 year before diagnoses
    - Late latent: Long term partners and children
    - Congenital: Assess mother and sexual partners

5. Risk reduction, health promotion, and prevention activities should be discussed with the patient.
   - Promotion of condom use

infections, such as rubella, cytomegalovirus infection, and toxoplasmosis.[2]

All pregnant women should be screened for syphilis with a non-treponemal serologic test on their first prenatal visit. If, on screening, evidence of syphilis is present, treatment should be initiated immediately according to the stage of disease. The optimal treatment of an infant born with congenital syphilis still not known.

What other treatment options exist for syphilis?

Treatment of syphilis in its early stages (primary or secondary) should prevent progression to later stages.

Table 2 summarizes the available treatments. For those who are penicillin allergic, an alternative treatment regimen, using azithromycin, may be administered during primary and secondary syphilis. However, there have been reports of therapeutic failures with the azithromycin regimen. Therefore, no matter what stage, penicillin remains the treatment of choice.

If a penicillin allergy exists during later stages, desensitization therapy should be considered. If a non-penicillin therapy is provided, it is imperative that followup serology be performed to ensure adequate treatment.

Is benzathine penicillin readily available?

The manufacturer of benzathine penicillin discontinued the distribution of injectable benzathine penicillin G (Bicillin L-A™) in Canada in January 2002. While Health Canada has been able to secure alternative sources of benzathine penicillin G for the short-term, it is uncertain what the long-term solution will be.

What public health interventions should be undertaken?

Prompt detection and treatment are essential to prevent the spread of syphilis. Table 3 outlines public health interventions for persons diagnosed with syphilis.

What followup is necessary?

Once syphilis has been diagnosed and treated, it is important to ensure treatment has been successful. Serial non-treponemal serologic tests, such as RPR or VDRL, should be obtained to monitor the patient's response to treatment. Table 4 demonstrates monitoring internals. A steady drop in titer

Take-home message

- The most well established technique for investigating active cutaneous lesions is dark field microscopy.
- Regardless of stage, penicillin remains the treatment of choice for syphilis.
- Since syphilis may mimic other conditions, it is still important to consider the disease in the differential diagnosis.

Table 4

Followup syphilis serology after treatment

Syphilis Stage	Time to obtain specimen
Primary, Secondary Early Latent, Congenital	1,3,6,12, and 24 months after treatment
Late latent, tertiary	12 and 24 months after treatment
Neurosyphilis	6, 12 and 24 months after treatment
If HIV infected	1, 3, 6, 12, and 12 months after treatment and yearly thereafter.

or stabilization to lower or non-detectable levels of non-treponemal test should be observed from the majority of patients over the proceeding two to three years. If a non-treponemal test titer increases fourfold after treatment, the patient should be carefully re-evaluated to ensure reinfection has not occurred. If not, a lumbar puncture should be performed.

Syphilis and HIV co-infection?

Genital ulcer disease can facilitate acquisition of HIV infection. In most people with early HIV infection, the clinical manifestations, serologic test results, and response to therapy are similar to those not infected with HIV. However, the manifestations of syphilis may be variable in those with advanced immunosuppression. Treatment modifications may be required in patients with advanced immunosuppresion from HIV. It may be prudent to confer with an infectious diseases physician or public-health official prior to starting treatment of a person co-infected with HIV and syphilis.

What is the jarisch-herxheimer reaction?

This is an acute febrile state characterized by chills, headache, and myalgia, occasionally observed within the first day after effective treatment for primary or secondary syphilis. The reaction usually resolves within 12 to 24 hours. Symptomatic relief may be achieved with antipyretic agents.[3]

Keep in mind...

Although syphilis was recently thought to have been eradicated in Canada, a recent resurgence in British Columbia and other provinces should heighten awareness that the threat of syphilis remains. CME

References

1. Golden MR, Marra CM, Holmes KK: Update on syphilis: resurgence of an old problem. JAMA 2003; 290(11): 510-4.
2. Tramont EC: Treponema pallidum (Syphilis). In: Mandell GL, Bennett JE, Dolin R (eds.): Mandell, Douglas, and Bennet's principles and practice of infectious diseases. Churchill Livingston, Philadelphia, 5th edition, pp 2474-90.
3. Health Canada. Canadian STD Guidelines 1998 Edition. Ottawa, Canada, Pages 150-9.

Further references available—contact ***The Canadian Journal of CME*** at **cme@sta.ca**.

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