

Syphilis: detection, diagnosis, optimal antibiotic use, and follow-up

English summary

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SUMMARY

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Introduction

Syphilis is a sexually transmitted and blood-borne infection caused by the spirochete bacterium *Treponema pallidum*, subspecies *pallidum*. If not adequately treated, syphilis can progress through different stages and affect several systems. Early syphilis, which includes the primary, secondary and early latent stages of the disease, is also referred to as “infectious syphilis” because of the risk of contagion present during these stages of the disease. Late syphilis is not transmitted sexually and includes both the late latent stage and tertiary syphilis. Neurological manifestations (neurosyphilis) can occur at any stage of the disease. According to the Public Health Agency of Canada, infectious syphilis is the third most reported notifiable sexually transmitted infection.

Because its clinical presentation can be mistaken for that of other health problems, including monkeypox (mpox), syphilis poses certain diagnostic challenges, particularly in the primary and secondary phases. Furthermore, there are certain challenges in detecting tertiary syphilis and neurosyphilis. The optimal use guide previously published by the Institut national d'excellence en santé et en service sociaux gives little space to the diagnostic approach, focusing primarily on the optimal use of drugs for the treatment of the infection according to the disease stage. Clinicians who are less familiar with sexually transmitted and blood-borne infections therefore have few reference tools to assist them in their diagnostic and therapeutic approach to syphilis. In the current context of a resurgence in the number of reported cases, it was considered advisable to carry out work on syphilis and to revise the guide's contents in light of the new available data and guidance documents in order to improve the information and guidance for the diagnostic process.

Methodology

A systematic search of the scientific literature published between January 2017 and June 2022 was conducted in the MEDLINE, Embase and Evidence-based medicine Reviews (Cochrane Database of Systematic Reviews) databases. As well, a manual search of the grey literature was conducted by consulting, among other things, the websites of learned societies in the field related to the topic of interest. Document selection, data extraction and the evaluation of the methodological quality of the selected documents were carried out independently by two scientific professionals. To contextualize Québec practice, a manual search of the literature was also done by consulting the websites of regulatory agencies, health technology assessment agencies, government agencies, professional associations and healthcare institutions. The official product monographs for Health Canada-approved antibiotics were consulted as well. The analysis and synthesis of the gathered data were performed by one professional and validated by another. The analysis was performed from the perspective of contextualizing Québec practice, using

mainly legislative, regulatory and organizational contextual elements specific to Québec and the perspectives of the various stakeholders consulted. An advisory committee consisting of health professionals from different specialties and areas of expertise was created to gather the stakeholders' perspectives. Lastly, the overall quality of the work, its acceptability and its applicability were assessed with external reviewers who are specialists in the field of interest and with future users who did not participate in the project.

Results

Upon the completion of the analysis of all the gathered data and the iterative process with the advisory committee's members, the following key findings and messages were considered to have the potential to support the harmonization of clinical practice and to better support health professionals in the management of individuals with syphilis.

Adequate screening can curb transmission

The significant resurgence in the number of cases of syphilis, including congenital syphilis, observed in Québec is of concern and requires vigilance on the part of clinicians. The multiple stages of syphilis and the variability of its clinical presentation make it challenging for health professionals to identify persons infected with *T. pallidum*. Furthermore, the spontaneous regression, in the absence of treatment, of the clinical manifestations of the early phase and the absence of symptoms (in the latency phase) are factors that add to the difficulty of identifying the infected individuals. Thus, adequate screening is necessary to properly identify, treat and follow individuals with syphilis. This is also essential for pregnant women, as appropriate screening and management can significantly reduce the occurrence of congenital syphilis.

An effective diagnostic approach is needed to determine the stage of the disease

The clinical presentation of syphilis is complex and varied, and a sound diagnostic approach is necessary to administer an appropriate treatment based on the stage of the disease. The diagnostic approach relies on both the history and clinical presentation and on serology results for determining the stage of the infection. This should include an assessment of the exposure risk, checking for a history of syphilis, including previous results and treatments, if any, and a careful physical examination to evaluate for mucosal lesions. Screening for signs or symptoms of neurological involvement is important for identifying and referring to specialized care those who potentially have neurosyphilis, for whom intravenous treatment is required.

A lumbar puncture is not always required

Performing a lumbar puncture to evaluate for cerebrospinal fluid abnormalities is not always required for diagnosing or treating neurosyphilis. According to the latest guidance documents, a lumbar puncture is unnecessary before treatment in a person with isolated ocular or auditory symptoms if there are confirmed ocular or auditory abnormalities on examination, reactive syphilis serology and no cranial nerve dysfunction or other

neurological abnormalities. Furthermore, recent studies have shown that the normalization of the serum nontreponemal antibody titres is predictive of the normalization of the cerebrospinal fluid parameters after neurosyphilis treatment. According to several guidance documents and clinical practice guidelines consulted, among immunocompetent persons, repeated cerebrospinal fluid examinations are therefore unnecessary in presence of an adequate serological and clinical response in patients with neurosyphilis.

Proper interpretation of serological test results is essential for management

The serological tests are based on the use of a treponemal test and a nontreponemal test, which are performed sequentially according to one of the two algorithms available in the local laboratory. The interpretation of the results of these tests is sometimes challenging and should be part of the diagnostic approach described above, to guide the choice of treatment.

Treatment must be prescribed according to the stage of the disease

Penicillin G is the preferred drug for treating all stages of syphilis. However, while a single intramuscular dose of benzathine penicillin G is sufficient to treat early syphilitic infection, three doses administered one week apart are required for the treatment of late syphilis. In the presence of neurological manifestations, including ocular or auditory manifestations, intravenous administration of aqueous penicillin G for 10 to 14 days is the recommended regimen.

If there is a history of allergic reaction to penicillin, the individual's allergic status should be carefully assessed. The allergy should be confirmed and the possibility of desensitization, followed by a first-line treatment, should be considered prior to the use of an antibiotic other than penicillin.

In the event of a benzathine penicillin G shortage or if penicillin is contraindicated, doxycycline can be used to treat early syphilis and late syphilis. In individuals with neurosyphilis, the use of ceftriaxone may be considered.

As with all other individuals, treatment of syphilis in those living with human immunodeficiency virus should be administered according to the stage of the infection. Although atypical signs of the infection or more rapid progression to neurosyphilis are possible, these are uncommon in persons with human immunodeficiency virus infection who are on antiretroviral therapy and therefore not immunocompromised.

Pregnant women constitute a special population

To limit the number of cases of congenital syphilis in pregnant women, it is essential to adequately screen for syphilis at least once and, if necessary, more than once during pregnancy and at delivery. Furthermore, it is important to administer a treatment appropriate for the stage of the disease as soon as possible to limit the risk of transmission to the fetus. Pregnant women with syphilis should receive specialized, multidisciplinary management that includes a fetal ultrasound to screen for congenital

syphilis. Early follow-up is also necessary to ensure an adequate response to treatment, and the partners should be identified and treated to avoid reinfection during the pregnancy. Lastly, prior to birth, a plan for the management of the newborn should be prepared in collaboration with the team of professionals involved in the delivery and neonatal follow-up.

A serological follow-up is essential

A serological follow-up is of paramount importance in the management of persons with syphilis. Not only does it enable the clinician to monitor the response to treatment and avoid unnecessary lumbar punctures in cases of adequate clinical and serological responses in those treated for neurosyphilis, but it also permits the detection of reinfections or possible treatment failure. Furthermore, it permits a more accurate interpretation of subsequent results.

Lastly, since syphilis is a complex disease that can affect different systems, rapid and effective multidisciplinary collaboration is sometimes required, as is a consultation or joint management with a specialist or experienced colleague.

Preventive interventions with the infected person and their partners complete the management process

As for any other sexually transmitted and blood-borne infection, the management of persons with syphilis should include education and advice on the infection and risk reduction. In addition, encouraging or providing other preventive measures is essential. Since syphilis increases the risk of contracting and transmitting the human immunodeficiency virus (HIV), HIV testing should be carried out if the individual has reactive syphilis serology. Also, pre-exposure prophylaxis should be discussed with individuals at risk for HIV.

Anyone with syphilis should also be counselled on the importance of informing their partners. The latter should undergo a clinical and serological evaluation and, in certain situations, be treated empirically at once, especially if they had sexual contact with someone with early syphilis or latent syphilis of undetermined duration in the 90 days preceding diagnosis.

Recommendations and clinical tool

Upon the completion of the work, and after the iterative process with the advisory committee's members, in which the scientific data, the information and the recommendations from the consulted literature, the contextual elements and the perspectives of different consulted stakeholders were triangulated, a series of recommendations were made. These recommendations, which are at the core of the report, are also summarized in the accompanying optimal use guide.

Conclusions

An undetected or inadequately treated infection can have a significant impact on the person's quality of life, including an increased risk of complications. Untreated infections are also contributing to the increasing prevalence of syphilis. Optimal management of individuals with syphilis is likely to influence the transmission of the disease and curb the resurgence currently observed in Québec. While not a substitute for clinical judgment, the updated optimal use guide should support practice by increasing clinicians' confidence in identifying individuals with syphilis, determining the stage of the infection, and select the appropriate treatment. The improved information on the management of individuals with neurosyphilis and pregnant women is intended to better support clinicians in the context of the resurgence of syphilis in Québec.

Lastly, the optimal use guide is a clinical tool that complements those developed by the Ministère de la Santé et des Services sociaux and the Institut national de santé publique du Québec. However, practice enhancement and harmonization will depend on:

- The dissemination of the optimal use guide stemming from this work;
- Adherence to the changes and the uptake of the recommendations by the health professionals concerned; and
- The promotion of the tool by the health and social services system's public health departments.

Update

The advisability of updating the recommendations will be assessed in four years from the date of publication considering the advances in the scientific data, the evolution of the clinical practices, the significant changes in the complementary contextual documents published mainly by the Ministère de la Santé et des Services sociaux or the Institut national de santé publique du Québec, and the health and social services system's needs.

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