Synoptic tables of sexually transmitted diseases: a practical approach to syphilis

Tabelas sinópticas de DST: uma abordagem prática da sífilis

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Mr. Editor,

In our dermatological practice, we, as many colleagues who are dedicated to similar specialties, see more and more patients with syphilis. This increase can also be observed in international as well as national publications, especially in the Epidemiological Bulletin of Syphilis published regularly by the Brazilian Ministry of Health. Public and, to a lesser extent, private health institutions have been trying to control the current epidemic. Universities and National Health Professional Councils have also addressed the issue. Medical associations, especially the Brazilian Society of Sexually Transmitted Diseases, have an important role in educational initiatives to disseminate knowledge and good practices for the prevention and care of people with syphilis.

However, if the difficulty in accessing health services was not enough, we frequently identify problems in the management of people with syphilis, including when the care is provided by specialists. One of the main issues detected is the interpretation of serological tests. This problem is caused either by the unfamiliarity with the foundations and peculiar biological dynamics of syphilis antibodies — in treated and untreated disease — or by the introduction of new tests.

We are aware of the plethora of current publications on syphilis; nonetheless, we believe that our work (Table 1) synthesizes the minimum knowledge necessary to care for most cases at different stages of the disease. We have included minimal clinical descriptions that can be found in different phases of the disease — i.e., primary, secondary, and tertiary. Despite being a helpful classification, we stress the fact that asymptomatic and paucisymptomatic cases do occur and are frequent. This situation is frequent in men but is particularly important in the case of women, when primary lesions and/or regional lymphadenopathy are seldomly seen. Laboratory tests are accompanied by sensitivities, and specificities and the expected results in each stage of the disease. Treatments are based on the classification of early or late syphilis, which are not always easy to differentiate. Additionally, elements related to the need for investigation of potential complications are presented. We call attention to the early complications, which are often not considered.

We hope that this modest collaboration — based on the care of patients who come to our services with inadequate management and on the needs of practitioners who consult us occasionally — can reduce the most common difficulties.

As always, we keep in mind Seneca's (4 BC-65 AC) quote "the advantage is reciprocal, because men, while teaching, learn."

SYNOPTIC TABLES OF SEXUALLY TRANSMITTED DISEASES: A PRACTICAL APPROACH TO SYPHILIS

Syphilis, caused by *Treponema pallidum*, is a polymorphic and multisystemic disease transmitted by sexual contact or by the mother with an active infection to the child at any stage of pregnancy. It can be completely asymptomatic, and, in this case, the diagnosis depends exclusively on serological tests and clinical and epidemiological history[1]. Despite the possibility of transmission through the transfusion of blood and blood products, adequate screening practically eliminates it. Biosafety standards eliminate the chance of transmission through needles and other injection equipment.

Its lesions, when they occur, are, usually painless. They can go unnoticed by the patient and/or the practitioner[2], especially when located in the interior of the vaginal, anal, or perianal regions or inside the mouth[3].

Important general notes regarding laboratory tests

Some laboratories mistakenly provide the result of the fluorescent treponemal antibody absorption (FTA-ABS) test in IgG and IgM fractions. This procedure does not offer information regarding the activity of the disease and causes extreme confusion. Positive IgG fraction results should be considered a diagnosis of active or past/treated infection, regardless of the IgM fraction result.

Positive rapid tests should be indicative of disease, unless recent treatment documentation is available. Postponing treatment while waiting for confirmatory tests is unacceptable[3]. Nonetheless, non-treponemal tests should always be requested for serological monitoring (see the column "follow-up and criterion of cure"). The venereal disease research laboratory (VDRL) and the rapid plasma reagin (RPR) can be equally used for follow-up. However, since their results have no perfect correlation, once one of them has been chosen, the follow-up should always use the same test. In addition, although non-treponemal tests can present false-positive results, we underline that this phenomenon is very rare. This consideration becomes much more relevant in the case of pregnant women. The occurrence of biological false-positive (BFP) results with medical conditions is rare. For instance, BFP is estimated to occur in 0.2–0.8% of non-treponemal tests[2].

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Table 1 – Synoptic tables of sexually transmitted diseases: a practical approach to syphilis.

Clinical classification	Signs and symptoms	Laboratory[4-6]	Classification WHO[7]	Treatment	Follow-up and criterion of cure
Primary	- Hard chancre (erosion/ulcer at the inoculation site, most often in anogenital regions); - Regional lymphadenopathy.	**Dark-field:** Se=74–86%; Sp=85–100%. - Generally unavailable. Disadvantages: need for immediate reading and observer-dependent. Currently, it is not routinely used for diagnosis[2]. **- PCR** (in the process of being established as a diagnostic tool): Disadvantage: does not produce results immediately. **Treponemal tests:** - Rapid tests – immunochromatography (RT) - MHA-TP: Se=45.9–88.6%; Sp=98.8–99%; - FTA-ABS: Se=70–100%; Sp=84–100%; - TPPA: Se=86–100%; Sp=95–100%; - CIA/CMIA: Se=98%; Sp=99%; - EIA/ELISA: Se=77–100%; Sp=99–100%. **NTT:** - VDRL: Se=74–87%; Sp=96–99%; - RPR: Se=77–99%; Sp=93–99%. - Low titers are expected	**RECENT** (up to 1 year)	First-line: - Benzathine penicillin G 2.4 million IU, single dose, IM (one ampoule in each buttock). Patients allergic to penicillin: - Doxycycline 100 mg, p.o., 1 tablet 2x/day, for 14 days. Contraindicated during pregnancy. Note: The only treatment considered appropriate during pregnancy is benzathine penicillin (after desensitization in a medical service with the capacity to treat anaphylactic events with advanced life support apparatus). Alternative treatments: - Ceftriaxone 1 g, IV or IM, 1x/day, for 10 days* (ref. 4)[9]; - Procaine penicillin G 1.2 million IU, IM, 1x/day, for 10 days. Note: The classification as early/late disease will define the treatment regimen. This classification is not always easy to establish. If the duration of the disease cannot be determined, it should be regarded as late and treated accordingly.	**Follow-up[5]:** - Diagnostic tests for HIV, hepatitis, urethritis, and cervicitis must be offered; - Treponemal tests should not be requested anymore. They are usually positive for life; - NTT should be requested for baseline and repeated every three months in the first year and every six months in the second year. Criterion of cure: - Reduction of two titers six months after treatment. - Modifications of one dilution should not be considered; - NTT may become non-reactive; however, they usually remain reactive in low titres; - Although the patient could theoretically be released from follow-up after two years, the fact of having had syphilis is an important risk factor. Thus, we recommend performing an NTT every 6 to 12 months if epidemiological information warrants it.
Early latency	Absence of signs and symptoms.	Serological results are expected to be similar to the primary phase.			
Secondary	- Mucocutaneous lesions; - Micropolyadenopathy (especially retroauricular and epitrochlear); - Constitutional signs and symptoms. Note: evaluate for neurological, ocular, and hepatic symptoms and/or signs. Meningovascular syphilis (stroke, myelitis) can occur in secondary syphilis and can be considered early neurosyphilis[2].	Treponemal tests[8,10]: - RT (immunochromatography); - MHA-TP: Se=90–100%; Sp=98.8–99%; - FTA-ABS: Se=92.8–100%; Sp=84–100%; - TPPA: Se=100%; Sp=95–100%; - CIA/CMIA: Se=100%; Sp=99%; - EIA/ELISA: Se=85–100%; Sp=99–100%. Non-treponemal tests - VDRL: S=100%; E=96–99%; - RPR: S=98–100%; E=93–99%. - High NTT titers are expected depending on the duration of the disease			

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Clinical classification	Signs and symptoms	Laboratory[4-6]	Classification WHO[7]	Treatment	Follow-up and criterion of cure
Late latency	Absence of signs and symptoms.	Results are expected to be intermediate between the secondary and tertiary phase	**LATE** (more than 1 year of evolution)	First-line: - Benzathine penicillin G 7.4 million IU, 2.4 million IM (one ampoule in each buttock) in three weekly doses. Patients allergic to penicillin: - Doxycycline 100 mg, p.o., 1 tablet 2x/day, for 28 days. Contraindicated during pregnancy. Note: The only treatment considered appropriate during pregnancy is benzathine penicillin (after desensitization in a medical service with the capacity to treat anaphylactic events with advanced life support apparatus). Alternative treatments: - Ceftriaxone 1 g, IV or IM, 1x/day, for 10 days* (ref. 4)[9]; - Procaine penicillin G 1.2 million IU, IM, 1x/day, for 14 days. Note: The classification as early/late disease will define the treatment regimen. This classification is not always easy to establish. If the duration of the disease cannot be determined, it should be regarded as late and treated accordingly.	Caution: Pregnant women should be treated as early as possible. Treatment is considered effective when its completion occurs up to 30 days before delivery. The serological follow-up should be carried out monthly until the end of the pregnancy.
Tertiary	- Gummatous syphilis: skin or any other organ; - Periostitis, osteitis, arthritis, synovitis, and juxta-articular nodules; - Cardiovascular: coronary stenosis, aortitis, and aortic aneurysm; - Neurological: meningitis, gummas of the brain or medulla, optic nerve atrophy, injury to the seventh cranial pair, psychiatric manifestations.	**Treponemal tests**[8,10]**:** - RT: similar to other treatments - MHA-TP: Se=97–99%; Sp=98.8–99%; - FTA-ABS: Se=83.7–97.6%; Sp=84–100%; - TPPA: Se=86.8–100%; Sp=95–100%; - CIA/CMIA: Se=100%; Sp=99%; - EIA/ELISA: Se=92.1–99.9%; Sp=99–100%. **Non-treponemal tests:** - VDRL: Se=37–97%; Sp=96–99%; - RPR: Se=73%; Sp=93–99%. Low or even non-reactive titers are expected			
Neurosyphilis	Symptomatic: Types of involvement: acute meningeal, parenchymal, and/or gummatous lesions. Signs and symptoms: - Headache; - Hypoacusis; - Visual changes: uveitis, vitritis, retinitis; - Psychiatric manifestations; - Meningism; - Focal signs according to the location of the lesions; - Gait changes; - Impairment of cranial pairs. - Involvement of the nervous system can occur at any time of evolution (it is not exclusive in late disease).	**Recommend lumbar puncture for**[6]**:** **HIV-negative individuals**: - Presence of signs or symptom is described in the previous column. - Abnormal serological response. **HIV-positive individuals:** - Any of the above. - Signs or symptoms of NS and/or - Asymptomatic individuals with RPR ≥1:32 and/or CD4 ≥200 (some authors recommend for all patients) **Abnormal CSF**: Reactive VDRL-CSF (high Sp, low Se) and/or leukocytes ≥5×106/L and/or >45 mg/dL protein); VDRL is the only test to be used to diagnose NS (RPR, TRUST, USR should not be used). FTA-ABS (high Se and low Sp). Can be used to rule out NS.		First-line: - Crystalline benzylpenicillin 18–24 million IU, 1x/day, IV, in doses of 3–4 million IU every 4 hours or by continuous infusion, for 14 days; - Procaine penicillin G 2.4 million IU, 1x/day, IM for 10 days, with probenecid; Alternative (except for pregnant women): - Ceftriaxone 2 g, IV, 1x/day, for 10–14 days.	- CSF examination every six months until normalization[6]; - Note: - CSF TPPA titres ≥1:640 was validated against CSF VDRL, TP PCR, and vision or hearing abnormalities. Sensitivities were 93.9%, 81.5%, and 85.2%; specificities were 97%, 93.8% and 93.3%, respectively. It was similar to the specificity of CSF VDRL[11].
Cardiovascular syphilis	- Asymptomatic (most cases); - Symptomatic: - Aortitis (70%): aneurysm, aortic valve insufficiency - Coronary ostium stenosis	Tests indicated for evaluation: - Electrocardiogram; - Echocardiogram and carotid ultrasosonography; - Chest X-ray (linear calcifications in the ascending aortic wall and aortic dilation).		First-line: - Benzathine penicillin G 7.2 million IU, IM. Three weekly doses of 2.4 million IU (1 ampoule in each buttock). Patients allergic to penicillin: - Doxycycline 100 mg, p.o., 1 tablet 2x/day, for 28 days.	Cardiovascular treatment according to diagnosed disease.

FTA-ABS: fluorescent treponemal antibody absorption test; IgG: immunoglobulin G; IgM: immunoglobulin M; RT: rapid test; VDRL: venereal disease research laboratory; RPR: rapid plasma reagin; TRUST: toluidine red unheated serum test; USR: unheated serum reagin; NTT: non-treponemal tests; Se: sensitivity; Sp: specificity; PCR: polymerase chain reaction; MHA-TP: microhemagglutination assay for *Treponema pallidum*; TPPA: *Treponema pallidum* particle agglutination assay; CMIA: chemiluminescence immunoassay; EIA/ELISA: enzyme immunoassay/enzyme-linked immunosorbent assay; IM: intramuscular; p.o.: orally; IV: intravenous; HIV: human immunodeficiency virus; NS: neurosyphilis; CSF: cerebrospinal fluid; CD4: T-lymphocytes cluster of differentiation 4;, ceftriaxone can also be used as an alternative for penicillin. TP: *Treponema pallidum*

Currently, laboratories that have a large number of samples tend to perform automated treponemal tests and use non-treponemal tests to confirm a positive result (reverse flowchart).

Participation of each author

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Conflict of interests

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