

Consensus

Brazilian Protocol for Sexually Transmitted Infections 2020: acquired syphilis

**Francisca Lidiane Sampaio Freitas^{[1],[2]}, Adele Schwartz Benzaken^{[3],[4]},
Mauro Romero Leal de Passos^[5], Ivo Castelo Branco Coelho^[6]
and Angélica Espinosa Miranda^{[1],[7]}**

[1]. Ministério da Saúde, Secretaria de Vigilância em Saúde, Brasília, DF, Brasil.

[2]. Universidade de Brasília, Programa de Pós-Graduação em Saúde Coletiva, Brasília, DF, Brasil.

[3]. Fundação de Medicina Tropical Doutor Heitor Vieira Dourado, Manaus, AM, Brasil.

[4]. AIDS Healthcare Foundation, Los Angeles, Califórnia, USA.

[5]. Universidade Federal Fluminense, Centro de Ciências Médicas, Niterói, RJ, Brasil.

[6]. Universidade Federal do Ceará, Faculdade de Medicina, Fortaleza, CE, Brasil.

[7]. Universidade Federal do Espírito Santo, Vitória, Brasil.

Abstract

The Clinical Protocol and Therapeutic Guidelines for Comprehensive Care of People with Sexually Transmitted Infections, published by the Brazilian Ministry of Health in 2020, includes updates concerning acquired syphilis. The document comprises rapid test use, safety and efficacy of benzathine benzylpenicillin, case follow-up, neurosyphilis clinical and laboratory management, approaching sex partners, assistance and monitoring of diagnosed pregnant women, and syphilis and HIV co-infection specificities, as well as a case notification summary. Health managers and professionals must be continuously trained so as to integrate care and surveillance, to strengthen actions for efficient control of syphilis, to broaden the search for sex partners, and to expand access of most vulnerable populations to health services.

Keywords: Syphilis. Clinical protocols. Diagnosis. Therapeutics.

Highlighted excerpt: Most people with syphilis are asymptomatic; this contributes to the maintenance of the transmission chain. Without adequate treatment of pregnant women with syphilis, severe consequences can occur, such as miscarriage, prematurity, low birth weight, natimortality, and congenital syphilis.

INTRODUCTION

This article summarizes the chapter on acquired syphilis, part of the Clinical Protocol and Therapeutic Guidelines (PDCT) for Comprehensive Care of People with Sexually Transmitted Infections (STI). The PDCT was approved by the National Committee for the Incorporation of Technologies to the Brazilian

National Health System (Conitec), through Ordinance no. 42, of October 5, 2018¹. When writing the Protocol, evidence available in literature for analysis was selected, and discussion among specialists was carried out. The PDCT was updated by the technical group and published in 2020 by the Health Surveillance Department of the Brazilian Ministry of Health.

EPIDEMIOLOGICAL ASPECTS

Syphilis is an STI caused by the *Treponema pallidum* bacteria, subspecies *pallidum*. Transmission is mainly sexual (oral, vaginal, or anal). It can also be transmitted vertically, with a fetal mortality rate higher than 40%².

Most people with syphilis are asymptomatic, which contributes to maintenance of the transmission chain. If the disease is not treated, it can lead to severe systemic complications after many years from the initial infection³⁻⁵. Without adequate treatment of pregnant women with syphilis, severe consequences can occur to the fetus or the conceptus, such as miscarriage, prematurity, low

Corresponding author: Francisca Lidiane Sampaio Freitas.

e-mail: lidianesfreitas18@gmail.com

 <https://orcid.org/0000-0003-1344-6389>

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birth weight, natimortality, and early or late clinical congenital syphilis manifestations⁶.

Treponema penetrates the mucous membranes directly or enters through skin injuries. Transmission is higher at the infection's early stages (primary and secondary syphilis), gradually decreasing over time⁵.

In 2016, the World Health Organization (WHO) estimated 6.3 million new cases of syphilis worldwide, with a 0.5% prevalence in men and women, and regional values varying from 0.1% to 1.6%⁷. In Brazil, a national study⁸ in 2016 showed a 0.6% syphilis prevalence in conscript young people, who were called for selection commissions, after the military enlistment stage. A high syphilis prevalence was observed in segments of critical populations in Brazil, such as men who have sex with men (9.9%)⁹, female sex workers (8.5%)¹⁰, and prisoners (3.8%)¹¹.

The acquired syphilis detection rate increased from 59.1 cases per 100,000 inhabitants, in 2017, to 75.8 cases per 100,000 inhabitants, in 2018, with a higher increasing trend among the population between 20 and 29 years, from 2010 to 2018, according to data from the Notifiable Diseases Information System (Sinan)¹².

CLINICAL ASPECTS

To guide treatment and clinical and laboratory follow-up, syphilis infection is divided into the stages of recent syphilis (primary, secondary, and recent latent ones) with one year of evolution, and late syphilis (late latent and tertiary ones), longer than a year⁴.

Figure 1 shows the clinical stages of acquired syphilis. At initial phases, symptomatology can vary and disappear, regardless of treatment. Clinical manifestations give room to clinical suspicion, but there is no exclusive signal or symptom; this can lead to

misunderstanding concerning other pathologies and make diagnosis more difficult¹³.

Central nervous system (CNS) involvement can take place at any stage of clinical syphilis¹⁴. Early neurosyphilis manifests immediately after syphilis infection and meningitis and abnormalities in the cranial nerves^{15,16}. Due to the era of antibiotics and the dominant use of beta-lactam antibiotics, neurosyphilis' clinical presentation has changed, with oligosymptomatic and atypical clinical pictures of the disease presenting increase¹⁵.

DIAGNOSIS

To diagnose syphilis, clinical data, results from diagnostic tests, previous investigation history, and investigation on recent risky sexual exposure must be combined¹⁷. Analysis of sexual history is relevant to diagnosis, and requires professional skills and confidentiality assurance¹⁸.

Direct examinations and immunological tests are also used for diagnosis of syphilis. Direct examinations are those in which *T. pallidum* research or detection in biological samples collected directly from primary and secondary lesions is performed¹⁹.

Immunological tests (treponemal and nontreponemal) are the most common in clinical practice for tracking asymptomatic people and diagnosing symptomatic patients⁵. Their characteristic is the research of total antibodies in whole blood, serum, or plasma (**Figure 2**). Although there is a synthesis of specific IgM antibodies at the initial infection phase, such antibodies are also found in late infection stages; therefore, IgM tests are not recommended on their own^{2,17}.

Treponemal tests detect specific antibodies produced against *T. pallidum* antigens. For example, rapid tests (immunochromatographic)

Stage	Clinical manifestations
Primary	Hard chancre (genital ulcer) rich in treponemas, generally single and painless, with a well-defined and regular border, hardened base, and clean background at the place of the bacterial entrance (penis, vulva, vagina, cervix, anus, mouth, or other integumentary places) Size increase and number of regional lymph nodes
Secondary	Skin-mucosa lesions (roseola, mucous plaques, papular syphilides, palmoplantar syphilides, flat condyloma, alopecia areata, madarosis, hoarseness) Micropoliadenopathy Generalized lymphadenopathy Constitutional signals Neurological, ocular, hepatic clinical pictures
Recent latent (up to one year)	Asymptomatic
Late latent (longer than one year)	Asymptomatic
Tertiary	Skin: gumma and nodular lesions, with destructive character Bones: periostitis, gumma or sclerosing osteitis, arthritis, synovitis, and juxta-articular nodules Cardiovascular: coronary stenosis, aortitis, and aortic aneurysm, especially in the thorax portion Neurological: meningitis, cerebral or spinal gummas, atrophy of optic disc, lesion of the seventh cranial pair, psychiatric manifestations, tabes dorsalis, and dementia, such as general paralysis

Source: Clinical Protocol and Therapeutic Guidelines for Comprehensive Care for People with Sexually Transmitted Infections, 2020¹³.

FIGURE 1: Acquired syphilis clinical manifestations and stages.

Immunological tests	Types	Notes
Treponemal	<ul style="list-style-type: none"> Rapid test (ex.: immunochromatographic) Indirect immunofluorescent test - fluorescent treponemal antibody-absorption (FTA-Abs) Enzymatic assays - enzyme-linked immunosorbent assay (ELISA) and its variations, such as chemiluminescence assays Haemagglutination tests -Treponema Pallidum Haemagglutination Test (TPHA) and particle agglutination - <i>T. pallidum</i> particle agglutination assay (TPPA); micro-haemagglutination assays - micro-haemagglutination assay (MHA-TP) 	<ul style="list-style-type: none"> The first ones to react. Keep reacting in most of the syphilis cases throughout life, regardless of treatment. Necessary for diagnosis but are not indicated for monitoring response to treatment.
nontreponemal	<ul style="list-style-type: none"> Venereal disease research laboratory (VDRL) Rapid plasma reagin (RPR) Toluidine red unheated serum test (TRUST) Unheated-serum reagin (USR) 	<ul style="list-style-type: none"> React around one to three weeks after hard chancre manifestation. The final result of these reacting tests must be expressed in titration, as per the last dilution presenting reactivity (1:2, 1:4, 1:8, etc.). Necessary for diagnosis and monitoring response to treatment.

Source: adapted from Clinical Protocol and Therapeutic Guidelines for Comprehensive Care for People with Sexually Transmitted Infections, 2020¹³.

FIGURE 2: Immunological test for syphilis diagnosis.

can be highlighted, and they do not need a laboratory structure. In around 85% of cases, treponemal tests keep reacting throughout life (serological scar), regardless of treatment¹⁹, which allows for differentiating an active infection from a past one⁵.

Nontreponemal tests, such as the venereal disease research laboratory (VDRL), detect anticardiolipin antibodies nonspecific for *T. pallidum* antigens¹⁹. They are semi quantitative tests, as, in case of reacting results, dilution of the sample for titration of these antibodies is performed². Such titration may vary, depending on the disease stage and on treatment or lack of it. Low titration (<1:4) of nontreponemal antibodies may be found in the infection's early and late phases, persisting for months or years. For this reason, there is no specific cut-point, and any titration must be investigated as syphilis¹³. Non-negativity of nontreponemal tests after treatment is called a serological scar. This event can be temporary or persistent, and it can present low or high titration, depending on the initial titration found at the moment of diagnosis^{4,17}.

Starting the investigation with a treponemal test, preferably the rapid test, is recommended due to its higher sensitivity^{2,17}. With the results, there are various combinations of treponemal and nontreponemal tests' use, with possible interpretation and respective conducts (Figure 3)^{13,17}.

Healthcare professionals, especially medical and nursing, must explain the purpose of immunological tests in the request form for the laboratory network. In the diagnostic approach, three different situations are considered: syphilis diagnosis, when there is no rapid test in the healthcare service; syphilis diagnosis, after reacting rapid test at the place of service; and treatment follow-up, when the diagnosis and treatment have taken place, and it is needed to monitor the nontreponemal antibody titration for cure control, preferably with the same method used for diagnosis¹³.

There is no gold standard test for neurosyphilis diagnosis. It is based on a combination of clinical findings, alterations in the cerebrospinal fluid (CSF), and results of nontreponemal testing in CSF. It is hard to find patients with neurosyphilis who do not present pleocytosis²⁰. Although levels of protein in CSF are not sensitive and specific to neurosyphilis diagnosis, protein standardization is essential for post-treatment monitoring²¹⁻²⁴.

TREATMENT

Immediate treatment is recommended, with benzathine benzylpenicillin, following a reacting - treponemal or nontreponemal - test for syphilis in the following cases, regardless of the presence of signs and symptoms:¹³ pregnant women; sexual violence victims; people with a chance of follow-up loss (those who will not return to the service); people with signs and symptoms of primary or secondary syphilis; and people without previous syphilis diagnosis.

After the first reacting test, treatment does not exclude the need for a second test, clinical and laboratory follow-up, and sex partners' diagnosis and treatment. There are specific therapeutic schemes as per the clinical classification of syphilis (Figure 4)¹³. Solving signs and symptoms after treatment indicates a response to the therapy. A post-treatment follow-up must be conducted after the nontreponemal test for determining the adequate immune response²⁵.

In order to guarantee availability of benzathine benzylpenicillin, it began to be acquired in a centralized way by the Brazilian Ministry of Health, as a strategic component of the pharmaceutical care in the Essential Medicines National List, from 2017²⁶. Notified syphilis cases (acquired and in pregnant women) served as a base for calculating purchase and distribution¹³.

Benzathine benzylpenicillin must be administered through an intramuscular route (IM)¹⁹. The ventrogluteal region is the

First test ^a + supplementary test	Possible interpretation	Conduct
Reacting treponemal test + reacting nontreponemal test or Reacting nontreponemal test + reacting treponemal test	- Syphilis diagnosis <ul style="list-style-type: none"> Classification of the clinical-stage to be defined according to the time of infection and treatment history. - Serological scar ^b	- When there is syphilis, treat, monitor with nontreponemal test and notify syphilis case. - When the serological scar is confirmed, guide only.
Reacting nontreponemal test + non-reacting treponemal test or Reacting treponemal test + non-reacting nontreponemal test	- Conduct a third treponemal test with a different methodology from the treponemal one already conducted. <ul style="list-style-type: none"> If reacting: syphilis or serological scar diagnosis. If not reacting: consider the result false reagent for the first test, excluding syphilis diagnosis. If the third treponemal test is not available, assess exposure to risk, signals, symptoms, and treatment history for defining the conduct. - Serological scar ^b	- When there is syphilis, treat, monitor with nontreponemal test and notify syphilis case. - When a serological scar is confirmed, guide only. - For cases concluded as lack of syphilis, guide only.
Non-reacting treponemal or nontreponemal test + do not conduct the complementary test if the first one does not react and if there is no clinical suspicion on primary syphilis	- Lack of infection or immunological window period ^c for recent syphilis.	- In case of clinical or epidemiological suspicion, request new sample collection within 30 days. - Avoid postponing treatment in case if the syphilis diagnosis is the most probable (ex.: visualization of anogenital ulcer) or in case if the return of the person to the healthcare service is not assured.

Source: adapted from the Clinical Protocol and Therapeutic Guidelines for Comprehensive Care for People with Sexually Transmitted Infections, 2020¹³.

Notes: a) Immediate treatment with benzathine benzylpenicillin after only one syphilis reacting test (treponemal or nontreponemal test) is indicated in situations described in item "Treatment", without exclusion of need for a second test for diagnosis definition; b) Documented previous treatment with titration drop in at least two dilutions; c) Immunological window: the period between infection and sufficient antibody production for immunological test detection.

FIGURE 3: Treponemal and nontreponemal test results, interpretation, and conduct.

Clinical classification	Therapeutic scheme	Alternative (except for pregnant women)	Follow-up
Recent syphilis: primary, secondary, and recent latent syphilis (up to one year of evolution)	Benzathine benzylpenicillin 2.4 million international units (IU), intramuscular (IM), single-dose (1.2 million in each gluteus)	Doxycycline 100mg, 12/12 hours, oral route (OR), for 15 days	Trimestral nontreponemal test up to 12 months of follow-up (in pregnant women, monthly control)
Late syphilis: late latent syphilis (with more than one year of evolution) or latent with unknown duration and tertiary syphilis	Benzathine benzylpenicillin 2.4 million IU, IM, once/week (1,2 million in each gluteus) for three weeks ^b Total dose: 7.2 million	Doxycycline 100mg, 12/12 hours, OR, for 30 days	Trimestral nontreponemal test up to 12 months of follow-up (in pregnant women, monthly control)
Neurosyphilis	Benzylpenicillin potassium (crystalline), 3 to 4 million IU, 4/4 hours, intravenous (IV) or continuous infusion, making up 18-24 million per day, for 14 days.	Ceftriaxone 2g, IV, once/day, for 10-14 days.	Cerebrospinal fluid examination of 6/6 months up to normal

Source: adapted from Clinical Protocol and Therapeutic Guidelines for Comprehensive Care for People with Sexually Transmitted Infections, 2020¹³.

Notes: a) Benzathine benzylpenicillin is the only safe and efficient option for adequate treatment of pregnant women. Any other treatment conducted during pregnancy, for purposes of defining the case and therapeutic approach of congenital syphilis, is deemed inadequate treatment for the mother; consequently, the newborn will be notified as having congenital syphilis undergo clinical and laboratory assessment; b) The interval between doses must not be longer than 14 days. In such a case, the scheme must restart¹⁹.

FIGURE 4: Treatment and follow-up of syphilis and neurosyphilis cases.

preferable place, as it is free from important vessels and nerves, and is a thinner subcutaneous tissue, which implies few adverse effects and less local pain²⁷. Thigh vastus lateralis and dorsogluteal regions are other options for application. When application through the IM route is unfeasible in the indicated places due to the presence of silicone (prosthesis or industrial liquid), alternative treatment through oral route is recommended (**Figure 4**)¹³.

Jarisch-Herxheimer reaction is an episode that can happen in the first 24 hours after starting treatment with penicillin, mainly in primary and secondary syphilis. Its manifestation exacerbates skin lesions with erythema, pain or pruritus, general discomfort, fever, headache, and arthralgia²⁸. Antipyretics can be used for controlling symptoms, but there is no evidence of reaction prevention⁴. People must be warned of the possibility of such benign and self-limited events²⁹, and, especially, of the distinction regarding allergy to penicillin³⁰.

According to a systematic review with meta-analysis, anaphylaxis risk in using benzathine benzylpenicillin was 0.002%, with the expectation of 0 to 3 cases of anaphylaxis per 100,000 treated patients of 13 studies. There was no anaphylactic reaction or death in the pregnant population due to the use of benzathine benzylpenicillin in 1,244 women, with a reported case of cutaneous rash³¹.

Adrenalin is the medicine chosen for anaphylactic reaction treatment. In this case, primary health care protocol recommendations regarding spontaneous demands and urgency and emergency must be followed³².

Healthcare professionals' fear of adverse reactions arising from penicillin, beyond sporadic anaphylactic reactions, contributes to the loss of the opportune moment for the treatment of people with syphilis; also, it maintains the infection transmission chain and the occurrence of congenital syphilis¹³. Nursing professionals are backed by the Federal Nursing Council on extensive administration of benzathine benzylpenicillin in primary health care^{33,34}.

From 80% to 90% of self-reported penicillin allergies are expected to be incorrect; it is challenging to differentiate reactions and disease symptoms in most cases³⁵. Some specific situations do not characterize allergies, such as gastrointestinal symptoms, headaches, pruritus, family history, and suspected reactions that occurred more than ten years ago. Clinical history must be detailed for risk stratification of allergy to penicillin and to obtain adequate information and correct practice definition, preventing unnecessary referrals for desensitization in a hospital environment³⁶.

Monitoring response to treatment is mandatory and must be performed throughout the outpatient healthcare network. The drop in immune response markers to *T. pallidum* evaluation uses as parameter the non-reacting nontreponemal test or the drop in titration in at least two dilutions within up to six months for recent syphilis and drop in titration in at least two dilutions within up to 12 months for late syphilis^{4,37-40}.

The earlier the diagnosis and treatment, the faster the circulating antibodies will disappear, with negativity of nontreponemal tests or stabilizing this titration as low. The titration record of this nontreponemal examination at the beginning of treatment will serve as the base for clinical and laboratory monitoring¹⁷.

The following are criteria of benzathine benzylpenicillin retreatment:¹³ lack of titration reduction in two dilutions within six months (recent syphilis) or 12 months (late syphilis) after adequate treatment (ex.: from 1:32 to 1:8), or titration increase in two or more dilutions (ex.: from 1:16 to 1:64), or clinical signs' and symptoms' persistence or recurrence.

In reinfection cases, investigation of neurosyphilis through a lumbar puncture in the general population is recommended when there is no risk of sexual exposure. For people living with HIV, an investigation is recommended in all retreatment cases, regardless of occurrence or not of new exposure. After adequate treatment, when a new risk of sexual exposure during the analyzed period is dismissed, the persistence of reacting results in nontreponemal tests, with previous titration drop in at least two dilutions, is called a serological scar, and does not characterize therapeutic failure¹³.

For neurosyphilis, all people presenting reacting VDRL in CSF must be treated, regardless of neurological or eye signals, and of symptoms. Those presenting non-reacting VDRL in CSF and biochemical alterations in CSF and presence of neurological or eye symptoms or changes in CNS image characteristic for the disease, since other diseases cannot explain such changes, must also be treated. Patients with an initial negative examination in CSF must undergo control fluid puncture as well after six months from the end of treatment (**Figure 4**)¹³.

In the case of CSF alteration persistence, retreatment with benzathine benzylpenicillin is recommended. In blood samples, the drop in nontreponemal test titration in at least two dilutions or seroreversion for non-reagent may be a parameter to be considered as a response to neurosyphilis, especially in an unavailable lumbar puncture scenario⁴¹.

SURVEILLANCE, PREVENTION, AND CONTROL

Acquired syphilis has been under compulsory notification in Brazil since 2010, as per Consolidation Ordinance no. 4, of September 28, 2017⁴². Such notification is mandatory for physicians, other healthcare professionals, or those responsible for public and private healthcare services providing care to patients⁴³. Thus, the need for timely notification of all cases to Sinan is reinforced to subsidize the formulation and implementation of public STI policies in Brazil.

Between 46% and 60% of the sex partners of people with syphilis (primary and secondary) are estimated to be infected⁴⁴. If there is recent exposure (up to 90 days), even in case the person presents non-reacting immunological tests⁴, the recommendation is the presumptive treatment with a single dose of benzathine benzylpenicillin 2.4 million international units (IU), IM (1.2 million IU in each gluteus). It must be stressed that the clinical assessment and laboratory follow-up are crucial¹³. The approach to the sex partners contributes to decreasing the infection burden in the community, tracking asymptomatic people, and identifying sexual risk networks⁴⁵.

For clinical and laboratory follow-up of people with acquired syphilis, nontreponemal test titration must be conducted every three months up to the 12th follow-up month (3, 6, 9, and 12 months).

This monitoring contributes to classifying the response to treatment, identifying possible reinfection, and establishing adequate conduct for each case¹³.

In most laboratory routines, nontreponemal tests are not automatized, which can cause a difference between readings when different methods are used or performed by more than one observer. Thus, variations in dilution titration (ex.: from 1:16 for 1:8) do not have clinical significance. Follow-up is recommended, as possible, using the same diagnostic method¹⁷.

In the PDCT chapter on acquired syphilis, there is a section on the clinical decision algorithm for syphilis in pregnant women management of (acquired and in pregnant women), with a recommendation summary for case screening, diagnosis, treatment, notification and clinical and laboratory monitoring¹³.

SPECIAL POPULATIONS AND SITUATIONS

Pregnant women

Pregnant women must be tested for syphilis at their first prenatal care appointment (ideally in the first three months), at the beginning of the third trimester, and at the hospitalization for giving birth, in case of miscarriage or natimortality or exposure to risk or sexual violence history. Clinical and laboratory monitoring with nontreponemal testing must be conducted monthly during pregnancy⁴⁶. After birth, this follow-up is trimestral up to the 12th follow-up month¹³.

It is crucial to assure pregnant women and sex partners' diagnosis and treatment and register the procedure on the prenatal care notebook. Such conducts contribute to avoiding that the newborn undergoes unnecessary biomedical interventions⁴⁶. It is also essential to stimulate the father's or partner's participation throughout the prenatal care process for strengthening healthy affection relations⁴⁷.

HIV infections

For all people living with HIV diagnosed with syphilis, appointments with specialists must be early in case of neurological or eye signals or symptoms, and lumbar puncture is a diagnostic imposition. Recommendations for lumbar puncture in people living with HIV to investigate neurosyphilis encompass the presence of neurological or ophthalmologic symptoms, evidence of active tertiary syphilis, and clinical treatment failure, regardless of sexual history¹³.

In HIV infections, syphilis clinical manifestations and therapeutic response can be distinct due to each person's immunity. The presence of multiple chancres, higher frequency of secondary lesions, and Jarisch-Herxheimer reaction can be highlighted^{48,49}. Diagnosis criteria and treatment of syphilis for people living with HIV are the same for people without HIV infection⁴.

The update of the PCTD chapter on acquired syphilis converges with the need to train health managers and professionals continuously, to integrate care and surveillance, strengthen effective syphilis prevention actions, tracking asymptomatic people, and case diagnosis, treatment, follow-up, and surveillance, in addition to broadening the search for sex partners, and expanding the access of the most vulnerable populations to the health services.

ORCID

Francisca Lidiane Sampaio Freitas – 0000-0003-1344-6389

Adele Schwartz Benzaken - 0000-0002-1656-5749

Mauro Romero Leal de Passos - 0000-0002-6183-7985

Ivo Castelo Branco Coelho - 0000-0002-2238-0388

Angélica Espinosa Miranda – 0000-0002-5556-8379

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AUTHORS' CONTRIBUTIONS

Freitas FLS, Miranda AE, Benzaken AS, Passos MRL, and Coelho, IVB contributed to the concept, designing the study, bibliographical review, writing, and reviewing the article. All the authors approved the final version and stated that they are responsible for all its aspects, including the assurance of accuracy and integrity.

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