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Guidelines

Prevention and management of syphilis in pregnant and perinatal women

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1. Introduction

The *Société de pathologie infectieuse de langue Française* (French-language society of infectious diseases) (SPILF) and the *Collège national des gynécologues et Obstétriciens français* (French national college of gynecologists and obstetricians) (CNGOF) has decided to draw up guidelines for the prevention and management of syphilis in pregnant women and neonates. Factors making this work necessary include the persistence of a high level of syphilis circulation in France, a worldwide resurgence of syphilis in pregnant women, and the seriousness of the infection for the unborn child.

These guidelines were drawn up in the following stages: (1) designation by the two partner societies (SPILF and CNGOF) of experts to develop and draft them; (2) elaboration of the questions to be addressed in the guidelines; (3) analysis of the literature by the bibliographers and the experts; (4) drafting of the evidence and recommendations for each question by the group as a whole, (5) text and proposed guidelines sent to a group of reviewers, (6) revising the final text by taking the reviewers' comments into account. The level of evidence of the guidelines set out in the text below corresponds to "expert opinion", given the absence of randomized trials or other high-level evidence in this population.

2. General information

2.1. Definitions and natural history

2.1.1. Syphilis

Syphilis is an infection caused by a spiral-shaped bacterium of the spirochete family, *Treponema pallidum* subsp. *pallidum* [1,2]. Four stages are defined by their clinical manifestations (Table 1). Syphilis **is early** if the onset of infection can be dated to less than one year before diagnosis, and **late** otherwise (more than one year or in the absence of dating).

2.1.2. Congenital syphilis

Congenital syphilis (CS) is syphilis acquired *in utero* or during birth. Depending on the onset of clinical signs, CS is said to have an **early onset** (before the age of two) or a **late onset** (any time thereafter).

2.2. Epidemiology

The World Health Organization (WHO) estimated the number of syphilis cases in people aged 15–49 years in 2022 at 8.1 million worldwide [3]. The number of adverse events linked to CS was estimated at 150,000 fetal losses, 70,000 neonatal deaths, 55,000 preterm births, and 115,000 children with a diagnosis of CS [3].

In France:

- The incidence rate of syphilis diagnoses in private medical laboratories was 3/100,000 women aged 15–49 years in 2022 [4].
- Incidence rose among women in France by 26 % between 2016 and 2018. This increase reached 116 % in the French overseas departments and regions (DROM) [5].
- Between one and seven cases of CS were reported per year between 2012 and 2018 [5], a third of them in the DROMs. This figure is probably underestimated [6]. There has recently been a major increase in the number of CS diagnoses in Western Guyana (151 cases between 2020 and 2023, i.e., 0.8 % of births), and in Reunion (108 cases from 2017 to 2022) [7,8].

2.3. Transmission modes

Syphilis is transmitted by **direct mucocutaneous contact**: contact of mucous membrane or injured or micro-abraded skin with a chancre (50 % risk of transmission) or with another active mucocutaneous lesion. The muco-cutaneous contagious period corresponds to the early phase (< 12 months after infection). Mucocutaneous contagiousness (including sexual contagiousness) ceases during the late latency phase (> 12 months). Nasal discharges ("snuffles") from infected neonates have been reported to be highly contagious [2,9–14].

Syphilis is also transmitted **via the blood-borne transplacental route**, as *T. pallidum* is present in the blood during early syphilis (primary and secondary) and intermittently during the latent phase (early and late).

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Table 1
Characteristics of syphilis acquired in adults or congenital in infants and toddlers [1,16,50].

Phase	Stage	Clinical manifestations	Time of onset	Usual duration	Course
Early (< 1 year)	**Primary**	Chancre: a small sore, typically single, well-limited, painless Constant but can go unnoticed Satellite adenopathies Neurosyphilis*	10–90 days after contamination (median 21 days)	2–6 weeks	Resolution possible even without treatment If left untreated, secondary syphilis develops in 25 % of cases.
	Secondary	Pleiomorphic systemic dissemination Maculopapular rash: roseola, etc. Mucosal ulceration(s) Adenopathies Condylomatous lesions Hepatitis Nephritis Ophthalmological lesions: uveitis, etc. Neurosyphilis* Fever	Usually 2–12 weeks after onset of chancre(possible for up to six months)	3–12 weeks	Resolution possible even without treatment In the absence of treatment, progression to tertiary syphilis in 30 % of cases
Late (> 1 year or unknown)	**Early latent** **Late latent**	Asymptomatic			In the absence of treatment, progression to tertiary syphilis in 30 % of cases
	Tertiary	Cardiovascular: aortitis	10–30 years 5–7 years		In the absence of treatment, death possible
		Neurological: – General paralysis; – *Tabes dorsalis*: degeneration of the posterior cords of the spinal cord.	10–20 years 1–45 years (median 15 years)		
		Skin and bones: Gums (granulomatous lesions)			

*Neurosyphilis can occur at any stage of infection, mostly during the first two years of syphilis.

Transmission from mother to child therefore occurs either *in utero* (hematogenous), **or *intrapartum*** through contact with contagious genital lesions. In the absence of maternal treatment, transmission depends on two factors:

– Gestational age: transmission begins at 16 weeks of gestation and increases with gestational age [15].

– Stage of syphilis: transmission is correlated with spirochetemia and is estimated at 60 %-100 % in primary or secondary syphilis, 40 % in the early latent phase [2,16] and 10 % in the late latent phase [15,17].

No data favor transmission via breast milk [16,18].

2.4. Complications of maternal syphilis for pregnancy and the unborn child

Pregnancy does not alter the incidence, semiology, natural history, or severity of maternal syphilis [2,11,19–21].

Possible complications if treatment is not well-managed include:

- Fetal loss (fetal death and late fetal loss) in up to 40 % of cases. The risk is greatest when maternal infection occurs between 16 and 20 weeks of gestation [2,17].
- Prematurity (24 %) [22]
- Birth weight < 2500 g (33 %) [2,22]
- Early or late-onset CS. Early-onset neonatal CS is lethal in 20 % of cases. Sensory and/or neurodevelopmental sequelae as well as malformations occur in 40 % of the surviving children [16,17,22–26]. Late-onset CS can also cause musculoskeletal and skin lesions.

3. How can congenital syphilis be prevented?

Prevention of congenital syphilis (CS) includes actions taken before and during pregnancy.

3.1. Prevention of syphilis in women of childbearing age

3.1.1. Sexual and reproductive health education

Available guidelines call for the provision of universal information on modes of STI transmission, prevention, and risk factors [4,27].

Most professional or learned societies consider the following to be risk factors for syphilis:

- Multiple sexual partners
- Unprotected or inadequately protected sexual intercourse (vaginal or anal penetration, or oral-genital intercourse)
- Sex work
- Rape
- History of STI or current STI diagnosis
- Current STI diagnosis in sexual partner(s)
- Migration, homelessness, or precariousness
- Drug use or partner(s) reporting drug use
- Person living in a place of deprivation of liberty [17,23,28–38]

3.1.2. Screening for syphilis in women of childbearing age

Medicoeconomic studies show the benefits of screening for syphilis to prevent CS, particularly in preconception consultations [17,39–41].

Available guidelines suggest that it should take place:

- In preconception consultation, in case of risk factor(s) [17,42]
- After risky sex, as soon as possible AND six weeks later [43]
- At least once a year in case of persistent risk factor(s) [3,17]

3.1.3. Screening of sexual partner(s)

Available guidelines recommend offering screening to the sexual partner(s) of a woman diagnosed with syphilis [17,28,34].

3.1.4. Prevention of congenital syphilis during pregnancy

The *Haute Autorité de Santé* (French national authority for health, HAS) recommends providing pregnant patients with information explaining the modes of STI transmission, their prevention, and risk factors during pregnancy [17,44].

Screening for syphilis is mandatory in France for all pregnancies [45]. **Ideally, it should be performed at the start of pregnancy, optimally before 10 weeks' gestation** [17,34,45,46]. The HAS recommends that it be repeated in the event of a change of partner [17,46].

Some guidelines recommend that this screening be repeated during the third trimester of pregnancy and at delivery in case of risk factors. [15,28,38,40]. HAS also recommends *postpartum* screening if none took place during pregnancy [17].

There are no French data concerning screening of the sexual partner (s) of a pregnant woman diagnosed with syphilis. Data from southern Africa show that infected partners are a major risk factor for reinfection in pregnant women, due to lack of reciprocal information between partners, absence of screening, lack of awareness of the diagnosis, and lack of treatment [34,47,48].

RECOMMENDATION 1: Preventing congenital syphilis: How to prevent congenital syphilis?

- **Inform women before and during pregnancy about how STIs are transmitted and how to** prevent **them.**
- **Offer syphilis screening to women of childbearing age with STI risk factor(s)** (*at least once a year in the case of persistent risk factor(s), at the preconception consultation, and after each high-risk sexual encounter).*
- **Screen for syphilis during all pregnancies, preferably before 10 weeks' gestation.**
- **Repeat syphilis screening during pregnancy in case of change of partner(s) and/or high-risk sexual relations.**
- **Tell the patient about the importance of screening her partner (s) in the event of risk factor(s) and of her possible treatment in the event of positive screening.**

4. Microbiological diagnosis of syphilis in pregnancy

4.1. Screening and diagnostic tools

4.1.1. Direct microbiological diagnosis

Direct diagnosis is reserved for specialized facilities. It can be performed on mucocutaneous lesions, neonatal nasal discharge, and placental and cerebrospinal fluid (CSF) samples [49,50]. European guidelines suggest PCR testing for *T. pallidum* DNA on chancres or skin lesions in patients with suspected primary syphilis before seroconversion [50].

4.1.2. Indirect microbiological diagnosis

Diagnosis is based on serologic tests: treponemal tests (TTs) and nontreponemal tests (NTTs). TTs are based on treponemal antigens, and NTTs on nontreponemal lipid antigens (e.g. cardiolipins and lecithins). These tests do not distinguish between syphilis and endemic nonvenereal treponematoses.

1) Treponemal tests.

The tests available in France are:

- **TPHA** (*T. pallidum* hemagglutination agglutination test, an automated quantitative test): these tests detect total antibodies (IgG + IgM) by agglutination of red blood cells sensitized with *T. pallidum* antigens. TPPA (*T. pallidum* particle agglutination assay) and TPLA (*T. pallidum* latex agglutination assay) have replaced TPHA and operate on the same principle.
- **EIA** (enzyme immunoassay) **and CMIA/CLIA** (chemiluminescent immunoassay/ chemiluminescent microparticle immunoassay): these procedures detect IgG and/or IgM directed against recombinant treponemal antigens.
- **Immunoblots and Western blots** detect IgG or IgM on strips containing *T. pallidum* antigens. Their specificity is better than that of TPPA, TPLA, EIA, and CMIA/CLIA. They can therefore be used to confirm positivity [49].

The FTA-abs (fluorescent treponemal antibody absorption) test is no longer used.

IgM detection does not determine the stage or progression of syphilis.

TTs become positive 5 to 15 days after appearance of the chancre. They remain positive regardless of the disease course and despite treatment. (Fig. 1). They cannot be used for therapeutic follow-up, or to diagnose reinfection [49,50]. False-positive TTs can occur, mainly in autoimmune diseases, Lyme disease, and pregnancy. They concern up to 0.2 % of pregnant women [51].

2) Nontreponemal tests (NTTs).

The tests available in France are:

- **VDRL**: Venereal Disease Research Laboratory test: the only NTT validated for the detection of antibodies in CSF [49].
- **RPR**: Rapid Plasma Reagin test: preferred to VDRL for detecting total antibodies in serum.

They are expressed in titers that correspond to the inverse of the last serum dilution with a positive reaction.

False-negative NTTs can occur with undiluted serum samples, particularly in early syphilis (due to the prozone phenomenon associated with excessive antibody concentration and saturation of antigenic sites). In the event of a positive TT, available guidelines recommend performing NTT on serum dilutions of up to 1:8 or 1:16 to avoid this bias [49,50].

False-positive NTTs account for up to 0.8 % of test results [50] and can be observed in many situations: pregnancy, autoimmune disease, antiphospholipid syndrome, infection, cancer, intravenous drug use, etc. The majority of false positives have low titers (≤ 4) [49].

NTTs become positive around five days after TTs (Fig. 1). They fluctuate as the disease progresses and remain positive with low titers in late latent infections. After treatment, they usually become negative within one to two years, but may remain positive for longer periods of time in some cases, particularly after treatment of latent syphilis [45,50].

3) Rapid diagnostic tests.

These qualitative immunochromatographic tests detect treponemal and nontreponemal antibodies in serum or whole blood in around 15 min [50].

The WHO does not recommend them for first-line screening when other diagnostic tests are available [40]. European guidelines suggest their use at the time of delivery when screening was not performed during pregnancy [50]. The HAS recommends their use for screening in high-prevalence populations [52].

4.2. National and international guidelines

4.2.1. First-line tests

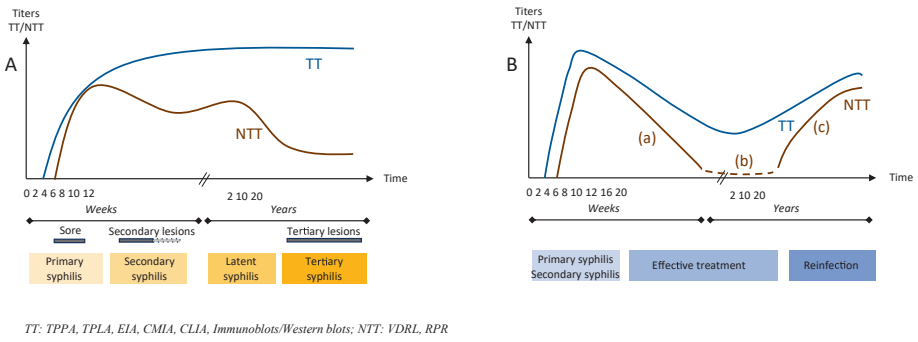
In the absence of clinical signs (screening situation), European, North American, and Australian guidelines call for TTs and/or NTTs [15,50,53,54]. The HAS guidelines in France recommend performing TT on total Ig (IgG + IgM) with a reproducible method (EIA and CMIA/CLIA) [45].

In the presence of a clinical sign, available guidelines call for immediate TT and NTT testing [45,50,55]. If these tests are negative, they should be repeated within three to five weeks [50,55] or three months [45].

4.2.2. Confirmation tests

Available guidelines call for a confirmatory test, specifically a quantitative NTT, to be carried out as a reflex test on the same serum if the first test is positive [50]. If these results are discordant (positive TT and negative NTT) and recent infection is not suspected, the HAS recommends repeating both the TT and the NTT one week later [45]. European recommendations in this situation call for TT to be performed a month later, and for TPPA-type TT to be preferred if the first TT was EIA or CLIA [50]. The available data do not allow us to prefer either one of these strategies.

If the TT and NTT are both positive in a pregnant woman, the HAS



TT: TPPA, TPLA, EIA, CMIA, CLIA, Immunoblots/Western blots; NTT: VDRL, RPR

Fig. 1. Course of serologic markers A. With no treatment, inadequate treatment, or nonsyphilitic treponematosis. B.If treatment is effective and reinfection occurs: (a) After effective treatment, NTT is reduced by a factor of four (two dilutions) after three months. This period may be prolonged in the treatment of late syphilis and in patients with uncontrolled HIV co-infection.(b) Some correctly treated patients retain weakly positive NTT, particularly if treatment begins late. (c) Reinfection results in multiplying the NTT by at least four. *TT: TPPA, TPLA, EIA, CMIA, CLIA, Immunoblots/Western blots; NTT: VDRL, RPR.*

recommends a systematic check of TT specificity by a reflex IgG immunoblot on the same serum.

In the absence of documentation of prior treatment, European guidelines recommend that anyone whose serology is interpreted as positive should be considered to have syphilis and should consequently be treated [50].

4.2.3. Diagnosis of neurosyphilis

The diagnosis of neurosyphilis does not exhibit any distinctive feature during pregnancy.

RECOMMENDATION 2: How to diagnose syphilis in pregnant women?

(Fig. 2**,** Table 2**).**

- **Order syphilis serology**

The prescription must mention the existence of pregnancy, contagion and/or clinical signs where applicable.

- **A positive TT must be immediately followed by a second TT (preferably immunoblot IgG) and a quantitative NTT (VDRL/RPR) on the same serum sample (reflex test).**
- **A full clinical examination must be performed for any positive TT.**
- **Interpretation of serology is based on comparison with data from patient history and** clinical **examination.**

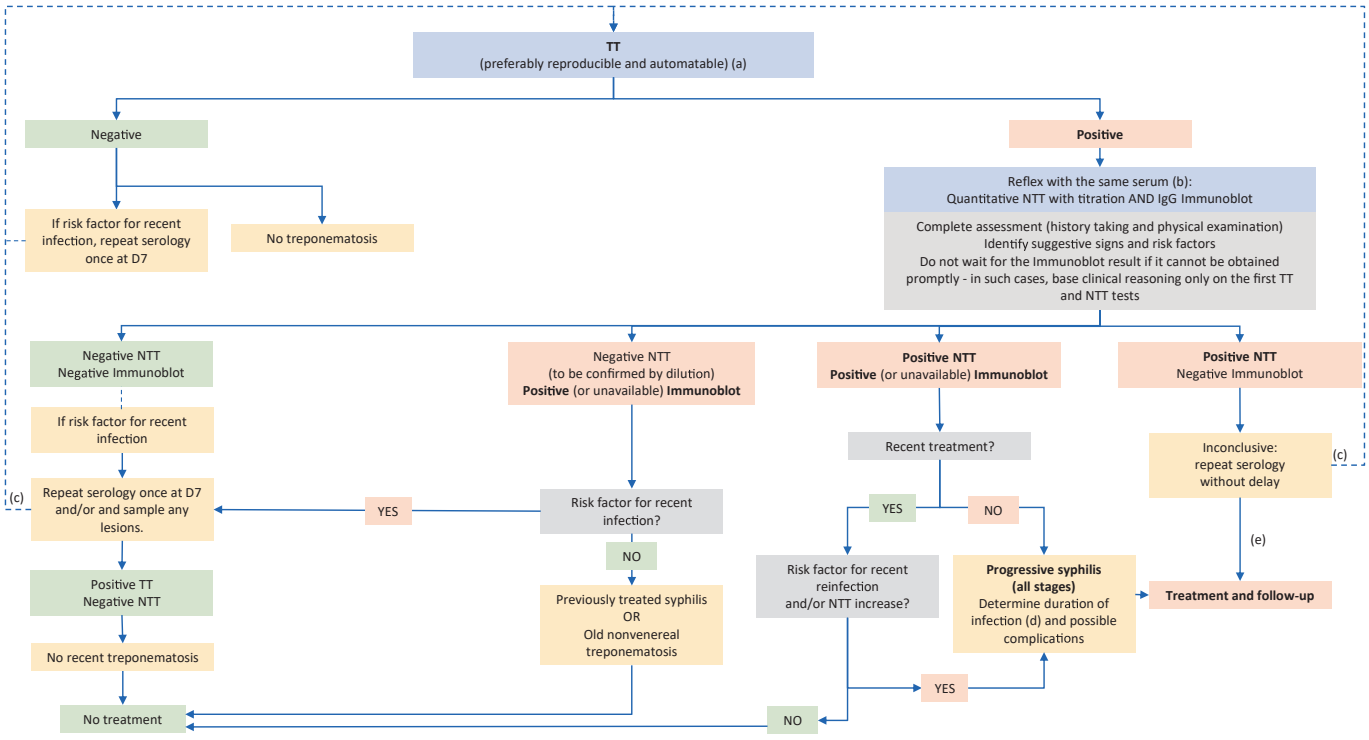


Fig. 2. Algorithm to interpret results of syphilis screening and diagnosis. (a) So that the laboratory can perform a confirmatory test (immunoblot), it is essential to specify on the prescription that the patient is pregnant. (b) These tests are generally carried out at the clinical pathologist's initiative. (c) Control serologic measurements should preferably be performed in the same laboratory. (d) Determination of infection duration is based on physical examination and questioning: history of syphilis in the patient or her partner, previous positive serology or documented seroconversion, treated syphilis. (e) When in doubt, begin treatment. *TT: treponemal test, NTT: nontreponemal test.*

Table 2
Interpretation of serologic diagnostic tests for syphilis and steps to take according to results.

TT (TPHA/ EIA/ CLIA/ CMIA, etc.)	NTT (VRDL/ RPR)	Confirmatory TT (Immunoblot)	Interpretation	What to do
Negative	Not performed	Not performed	No treponematosis OR Very recent infection (before seroconversion)	Repeat serology if risk factor for recent infection: - During pregnancy: at D7; - No pregnancy: within 3 months or earlier if pregnancy is desired.
Positive	Negative *Negativity to be confirmed by serum dilutions*	**Positive**	Early primary syphilis OR Previously treated syphilis OR Old nonvenereal treponematosis	Repeat serology on D7 if risk factor for recent infection *A mucosal lesion, if present, can be sampled for PCR* ***Important information:*** ***– Check that a prozone* effect on NTT has been ruled out (by serum dilutions);*** ***– Seek advice from the CNR if recent infection is suspected in a pregnant woman.***
Positive	**Positive**	**Positive**	Progressive syphilis, all stages OR Recently treated syphilis	Treatment (unless recent treatment AND absence of risk factor for recent infection AND no NTT increase)
Positive	Negative	Negative	Very recent infection (before NTT seroconversion) OR Previously treated syphilis OR False positive TT	Repeat serology in case of recent infection: - During pregnancy: at D7; - No pregnancy: within three months or earlier if pregnancy is desired. *If symptoms and 2nd NTT positive at D7:* primary syphilis *If second TT negative at D7:* initial TT was a false positive of initial TT
Positive	**Positive**	Negative	Inconclusive	*If second TT positive at D7:* see the line: "TT positive; NTT negative" Repeat serology without delay

*Prozone effect: when a serologic test is a false negative due to too high a concentration of antibodies in the sample.
TT: treponemal test; NTT: nontreponemal test; TPHA: T. pallidum *hemagglutination test; EIA: enzyme immunoassay; CLIA: chemiluminescence immunoassay; CMIA: chemiluminescent microparticle immunoassay; VDRL: Venereal Disease Research Laboratory test; RPR: rapid plasma reagin test; CNR: Centre national de référence (National Reference Centre)*.

Table 3
Main ultrasound, clinical, and laboratory signs in favor of fetal infection or congenital syphilis [31].

Ultrasound signs of CS	Signs of early CS	Signs of late CS
Fetal signs:	*Often not visible at birth (most often appearing within 4 weeks of birth)*	
Fetal growth restriction		Craniofacial deformities (frontal humps, square skull, saddle nose, short maxilla, high palate)
Hepatomegaly	Clear or bloody rhinorrhea ("snuffles"), laryngitis	Osteoarticular: saber shins, Higoumenakis sign (sternoclavicular thickening), Clutton joints (symmetrical, painless hydrarthrosis of elbows and knees)
Splenomegaly	Cutaneous: petechiae, flat or bullous skin lesions predominating on palms and soles, rhagades (chapped or linear wounds).	Rhagades (chapped skin or linear wounds)
Intestinal hyperechogenicity	Visceral: hepatosplenomegaly, adenopathy,	Abnormalities of permanent teeth: Hutchinson teeth (notched incisors with discolored enamel), mature molars, enamel hypoplasia
Effusions: ascites, subcutaneous edema, pericardial effusion	hepatitis, jaundice, ascites, pulmonary fibrosis (*"pneumonia alba"*), myocarditis, pancreatitis, nephrotic syndrome	Neurosensory: interstitial keratitis, deafness, mental retardation, hydrocephalus, cranial nerve damage
Anemia (increased flow in the middle cerebral artery)	Neurosensory: meningitis, uveitis, cataracts, glaucoma, chorioretinitis, corneal scarring, deafness, cranial nerve damage	Paroxysmal cold hemoglobinuria
Microcephaly	Osteoarticular: osteitis (long bones striated like celery sticks), osteochondritis, arthritis, periostitis, Parrot's pseudoparalysis (pain linked to periostitis), dactylitis.	Hutchinson triad: dental anomalies, deafness, and interstitial keratitis
Subcutaneous edema – hydrops	Anemia, thrombocytopenia, leukopenia	
Adnexal signs:		
Oligo/hydramnios		
Thickened placenta		

CS: congenital syphilis.

5. Maternal and obstetric management of syphilis during pregnancy

5.1. Pretreatment maternal assessment

5.1.1. Staging and extension assessment

Learned societies suggest adapting treatment to the stage of syphilis and to possible neurosyphilis [15,40,50,53,54,56,57].

5.1.2. Assessment of the risk of maternal allergic reaction to penicillin

Algorithms are available for the general population to assess the risk of allergy and guide appropriate investigations. No specific tool exists for pregnant women [58–61]. An algorithm in the European guidelines distinguishes six situations (Fig. 3) [62]. Three of them do not require referral to allergy specialists:

- Situations not to be considered as allergies: isolated minor reactions such as headache, diarrhea or vaginal mycosis, or a family history of allergy.
- Situations with a low risk of a new allergic reaction to penicillin, with no increased risk of severe reaction. Reintroduction of penicillin may be considered from the outset under medical supervision, with skin testing optional in this situation [62,63].
- Situations at high risk of delayed severe skin reaction contra-indicating any re-exposure to beta lactams (including reintroduction tests, skin tests, tolerance induction, and treatment) [64,65].

In other situations (low-to-intermediate risk, intermediate risk and high risk of immediate severe reaction), specialist investigations are indicated in the general population. In France, it is not always possible to consult an allergist within a time frame compatible with urgent maternal-fetal care.

5.2. Maternal treatment

5.2.1. First-line treatment

Benzathine penicillin G (BPG), a long-acting-acting penicillin G administered intramuscularly (IM), has a half-life of 14 days [66]. Its transplacental passage has been demonstrated by assays in amniotic fluid and cord blood [67]. A prospective cohort of 340 pregnant women evaluated the benefit of BPG treatment: 2.4 million IU for early forms (n = 204) and 7.2 million IU over a 3-week period for late forms (n = 136). Treatment efficacy for maternal infection was 99.7 %, and for CS prevention 98.2 % (204 women treated before 25 weeks) [68]. BPG treatment has also been shown to reduce the risks of prematurity [69] and of both fetal and perinatal death [69,70]. Learned societies recommend it as first-line treatment for syphilis in pregnant women, except for neurosyphilis [38,50,55,56].

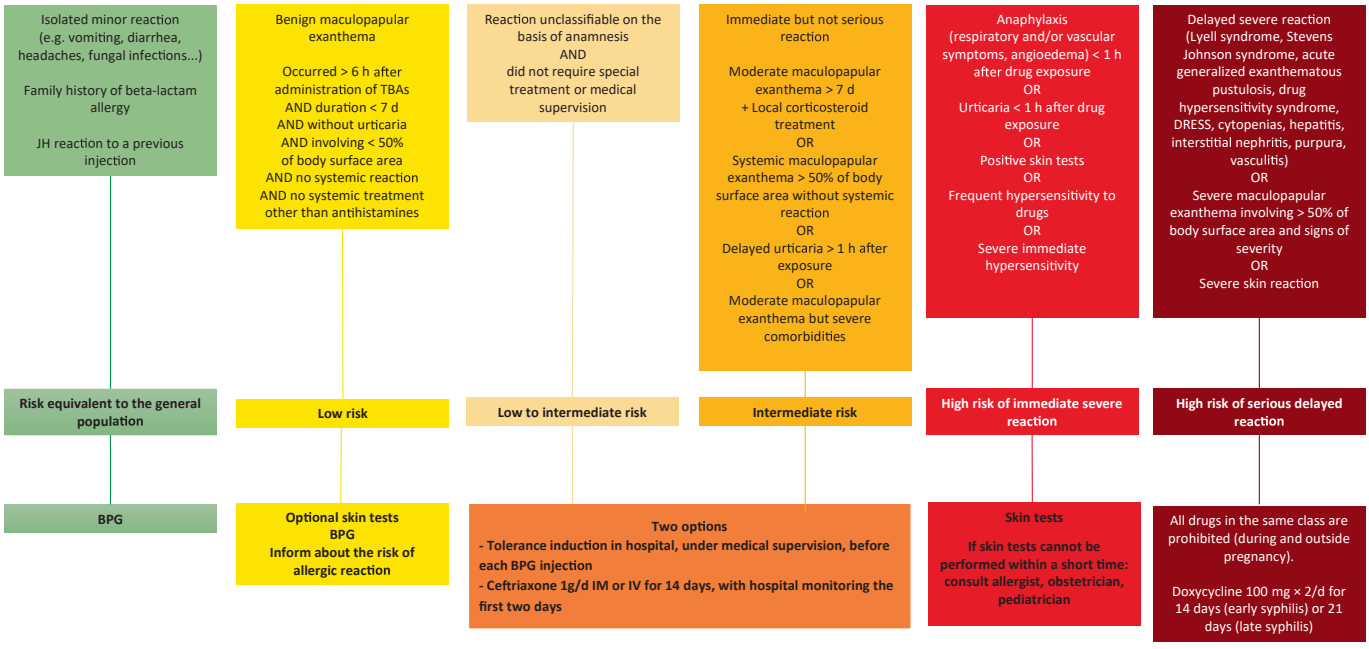
Benzylpenicillin (penicillin G, either IV or IM) is the historic antibiotic for syphilis, with proven efficacy [71], including in the treatment of neurosyphilis [72,73]. A noncomparative study evaluated the overall efficacy of different treatments in 2817 pregnant women receiving either three injections of BPG IM, benzylpenicillin at a dosage of 0.8 million IU IM per day for 14 days, or azithromycin 500 mg × 2 daily for 14 days, with an all-molecule effectiveness of 99.1 % in preventing CS [74]. The study did not confirm the noninferiority of benzylpenicillin versus BPG, as it did not compare the effectiveness of individual substances; moreover, the rate of loss to follow-up was 15 %, and the definition of CS was approximate. Nor do the data in the literature allow us to establish the optimal dosage of benzylpenicillin for the treatment of syphilis in the general population, *a fortiori* in pregnant women [50]. Daily administration of benzylpenicillin is restrictive. It is the first-line treatment for neurosyphilis and is recommended as a second-line treatment if BPG is unavailable in other situations [50,57].

To date, no clinical trial has compared the efficacy of BPG or benzylpenicillin with that of **another penicillin**, particularly an **oral** one. A single retrospective study of 80 women suggests that the effectiveness of ampicillin or amoxicillin in preventing CS is inadequate (21 % failure rate) [75].

5.2.2. Dosages

Early syphilis (primary, secondary, early latent < 1 year).

In the general population, treatment of early syphilis is based on a single dose of 2.4 million IU of BPG. No clinical trials have compared the



IM: intramuscular; IV: intravenous; BPG: benzathine penicillin G; JH: Jarisch-Herxheimer reaction; DRESS: drug reaction with eosinophilia and systemic symptoms.

Fig. 3. Assessment of allergic risk to beta-lactam antibiotics and suggested management of syphilis in pregnant women. *IM: intramuscular; IV: intravenous; BPG: benzathine penicillin G; JH: Jarisch-Herxheimer reaction; DRESS: drug reaction with eosinophilia and systemic symptoms.*

efficacy of one or two doses of BPG in reducing CS risk. Two prospective cohorts have studied different BPG dosages in pregnant women, but their protocols were quite different (number of doses, dosage per injection) and did not take confounding factors (stage of syphilis, gestational age at the time of treatment, ultrasound signs of possible CS, NTT titer) into account. The first cohort of 180 pregnant women showed higher rates of prematurity and perinatal death in the women who were not treated as well as those treated with a single dose of 2.4 million IU BPG, compared with women treated with two or three doses [76]. The same study compared the rates of CS according to the estimated duration of effective treatment and showed that the CS risk was higher in infants of mothers whose antibiotic coverage lasted less than three weeks. However, these findings were not based on any pharmacological assay [76].

Another cohort of 1470 pregnancies found that the CS risk declined by a factor of four after complete treatment, defined as two doses of 4.8 million IU BPG one week apart (n = 1319), compared with an unspecified incomplete treatment (n = 392) [77]. A retrospective study of 85 women with syphilis in French Guyana investigated factors associated with CS. It found a lower rate of CS in women who had received at least two doses of BPG compared with those who had received a single dose or no treatment at all (31 % vs. 77 %). However, there was no adjustment for other risk factors for CS, and 76 % of the women had received late treatment, less than a month before delivery [6].

Physiological changes (hemodilution, increased renal elimination) in the second half of pregnancy may induce **decreased plasma BPG concentration**, and penicillin concentrations vary more as the pregnancy advances [67]. Another study found supratherapeutic levels for at least 30 days in all women having received two injections of BPG [78].

There are no data on optimal dosage for pregnant women with obesity [79].

Different learned societies propose various treatment regimens for pregnant women:

- *Regimen with two injections of 2.4 million IU BPG* [15,80], particularly in case of ultrasound signs of CS [15,55,56] and/or after 20 weeks of gestation [15] or during the third trimester [53,56].
  - *Regimen with one dose of 2.4 million IU BPG* [40,50,54] with the possibility of administering 1.2 million IU in each arm [53,55,56].

Late syphilis (late clinical, late latent > one year, or impossible to date).

No study has compared treatment regimens for late syphilis in pregnant women, and no specific treatment recommendation exists for this situation. In the general population, the recommended treatment is an IM injection of 2.4 million IU of BPG, once a week for three weeks [15,55,57]: the interval between two doses should be seven days, and not exceed nine days [15]. If the interval exceeds nine days, a complete regimen should be repeated [15].

Neurosyphilis.

There are no studies evaluating the treatment of neurosyphilis in pregnant women, and no recommendations specific to this situation [81].

5.2.3. Treatment of women allergic to penicillin

Ceftriaxone.

According to the most recent data, the risk of cross-allergy to third-generation cephalosporins is less than 2 % [82,83]. Minimum inhibitory concentrations of ceftriaxone on *T. pallidum* are similar to those of penicillin G [84]. Studies in the general population have shown the non-inferiority of ceftriaxone versus BPG for the treatment of syphilis, whatever its stage (series of 230 patients [85] and *meta*-analysis of 115 patients [86]. Recent data suggest that the effectiveness of IV ceftriaxone at a dose of 2 g daily for at least 10 days in neurosyphilis is similar to that of BPG (n = 365) [87,88].

Data for pregnant women are very sparse. A retrospective study of 79 pregnant women showed that ceftriaxone at a dose of 250 mg or 500 mg IM daily for 10–14 days was effective in treating the mother, with no reported adverse effects, but its effectiveness in preventing CS was not assessed [89]. A therapeutic trial involving 11 penicillin-allergic pregnant women treated before 18 weeks' gestation with ceftriaxone IM 250 mg daily for seven days in the primary stage and 10 days in the secondary stage, with the same regimen repeated at 28 weeks' gestation, demonstrated efficacy for both mothers and children (no case of CS among the nine neonates not lost to follow-up) [90]. An isolated observation describes the effectiveness of treatment with ceftriaxone 250 mg daily IV for 10 days at 12 weeks' gestation and repeated at 28 weeks [91]. Available pharmacologic data show transplacental passage of ceftriaxone of 50 % at term [92].

Some learned societies recommend ceftriaxone as an alternative substance for patients allergic to penicillin at a dosage of 1 g per day IM for 10–14 days in the general population [54,57] and for pregnant women [40,56].

Doxycycline.

In the general population, despite its lesser effectiveness, doxycycline is a therapeutic alternative in cases of beta lactam allergy, at a dosage of 200 mg per day for 14 days [50,55 86]. A few observations of pregnant women allergic to penicillin and treated with doxycycline (100 mg twice a day for 14 days) have reported it to be effective for both mother and child [93,94]. Recent data raise questions about doxycycline's toxicity and teratogenicity for fetal bone and dentition, and its use remains contraindicated or advised against from the second trimester onwards [95] by many learned societies due to its structural similarity to tetracycline, which is associated with tooth enamel staining and possible deleterious effects on bone growth [57,95–97].

Macrolides.

In the general population, early studies showed the efficacy of macrolides for treatment of syphilis [98]. However, 85 % of *T. pallidum* strains now carry the A2058G mutation conferring resistance to this family [99]. Transplacental passage of macrolides is low (< 5 %), making it impossible to reach therapeutic concentrations for fetuses [100]. A high rate of CS has been reported under well-conducted maternal macrolide therapy [34,101]. Several learned societies consequently recommend against their use in this situation [56].

Tolerance induction in pregnant women allergic to penicillin

Tolerance induction corresponds to the reintroduction of penicillin in progressive doses, up to the therapeutic dose [102]. Each administration of the treatment requires a new induction of tolerance. In the general population, there is a 6 % risk of a serious adverse event during this procedure [103]. It is contraindicated in cases of history of delayed severe allergic reaction, and must in all cases be performed in a hospital and be supervised by a specialized medical team [104,105]. Induction of penicillin tolerance during pregnancy has been reported in several small series [93,105,106]. Two series of 91 [107] and 71 women [93] noted serious side effects in 2–20 % of cases, including anaphylaxis (1/91 and 2/71), generalized rash (1/91), and urticaria (2/71) [93,107].

European, U.S., and Canadian guidelines propose tolerance induction as the only therapeutic alternative in cases of suspected allergy to penicillin in syphilis during pregnancy [15,50,53]. Recent British guidelines place it on a par with ceftriaxone [56].

5.3. Processing methods

5.3.1. When to treat?

The evidence available in the literature is in favor of immediate treatment. Maternal-fetal transmission has been described as early as 16 weeks' gestation. Several studies suggest that BPG is more effective in reducing the risk of CS if administered before 28 weeks [108–111]. A time lapse of less than one month between treatment and delivery is associated with an increased risk of CS [6,112,113]. Some learned societies recommend treatment as early as the first trimester [54], others before 28 weeks of gestation [28], and some require a minimum of 30 days between treatment and delivery [38,50].

*5.3.2. Analgesic treatment associated with **BPG** injection*

European guidelines [50] and those of the *Société française de dermatologie* [55] suggest adding non-adrenalized lidocaine to BPG. Data concerning the use of lidocaine during pregnancy are reassuring [114]: its systemic diffusion after IM injection is very low.

5.3.3. Prevention of the Jarisch-Herxheimer (JH) reaction

The JH reaction is characterized by fever, myalgias, and arthralgias, occurring within 24 h of antibiotic administration [50,56,115–117]. It has been described in 55 % to 95 % of patients with primary syphilis and 95 % of those with secondary syphilis, but is very rare in late infections in the general population [118,119]. In adults, it resolves spontaneously without complications within 12 to 24 h [2]. Its incidence does not appear to be higher in pregnant women than in the general population, but its occurrence may be associated with uterine contractions (40 %-65 %), fetal heart rate abnormalities (40 %), and decreased active fetal movements [19,116,119].

In the general population, prevention of the JH reaction is based on the administration of acetaminophen [2], at times combined with anti-inflammatory treatment [50,55]. Corticosteroid therapy is associated with reduced occurrence of fever [120]. No study has evaluated the benefit of preventing this reaction in pregnant women, and no guideline proposes it systematically. The U.S.A. Centers for Disease Control (CDC) recommends that patients be informed of potential adverse reactions after treatment and of the need to seek medical advice without delay [15]. British guidelines recommend against the routine use of corticosteroids in pregnant women in this situation [56].

RECOMMENDATION 3: Indications for treating syphilis in pregnant women (Fig. 2).

Treatment is indicated in the following situations:

- **Syphilis confirmed by serology with positive TT and positive NTT**
- **Neurosyphilis confirmed by one of the following tests: positive blood TT and NTT associated with one of the following criteria:**

CSF cellularity ≥ 5 cells/mm^3 or positive NTT in the CSF or PCR amplifying *T. pallidum* DNA in the CSF

A positive TT with a negative NTT does not warrant any treatment.

RECOMMENDATION 4: Which maternal evaluation before treatment?

During a consultation devoted to this issue:

- **Apprise the patient of the diagnosis and its implications for the fetus**
- **Inform the patient about how syphilis is transmitted**
- **Classify infection** (early or late, presence or absence of neurosyphilis) before initiating treatment
  - Consider syphilis to be late stage in the absence of any conclusive stage information
  - Explore neurologic or sensory impairment if neurologic, visual or auditory symptoms appear to be present
- **Search for other STIs**
- **Assess the risk of maternal allergy to penicillin or cephalosporins** (Fig. 3)

RECOMMENDATION 5: Which maternal treatment?
(Fig. 4).

First-line treatment

- **Early syphilis: two doses of BPG 2.4 million IU IM one week apart**
- **Late syphilis: three doses of BPG 2.4 million IU IM one week apart**
- **Neurosyphilis: benzylpenicillin 20 million IU/day IV for 14 days**

Pregnant women allergic to penicillin (Fig. 3)

1) Low-risk **situations and risk equivalent to the general**

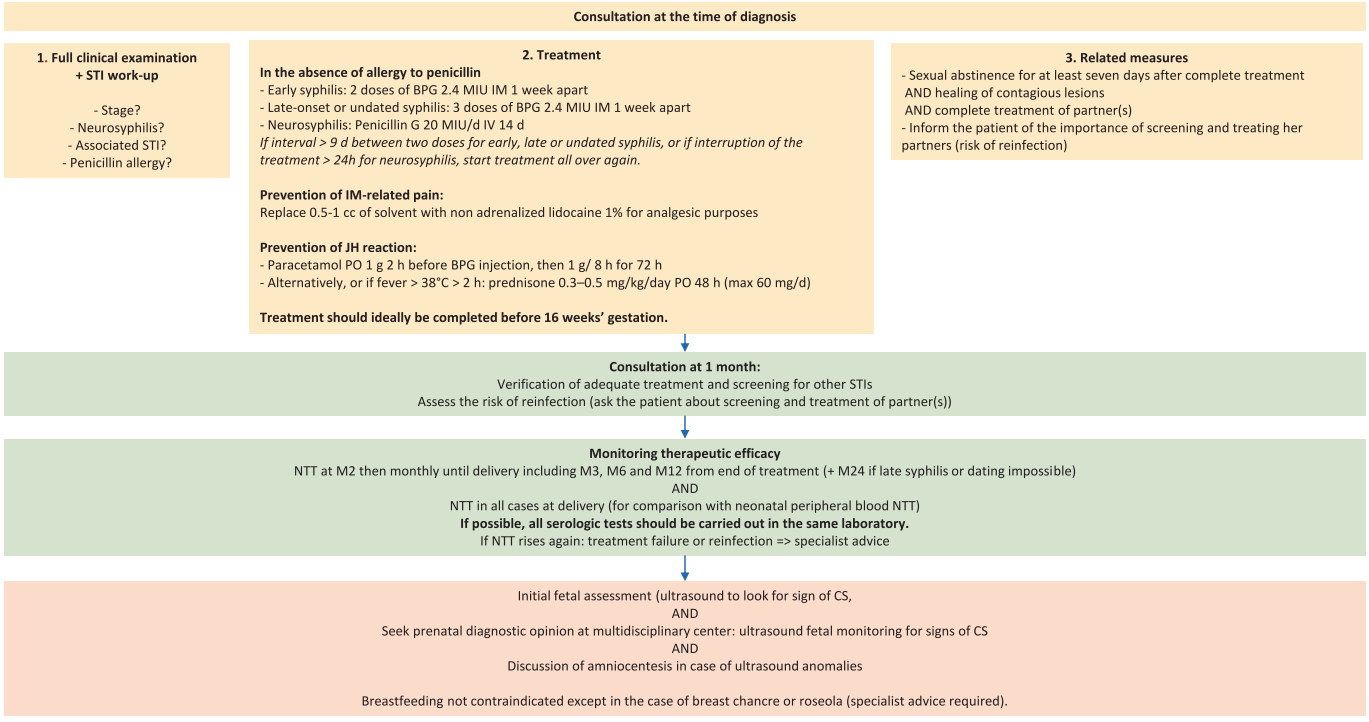


Fig. 4. Treatment and follow-up of syphilis in pregnant women. *BPG: benzathine penicillin G; CS: congenital syphilis; IM: intramuscular; IV: intravascular; M: month; JH: Jarisch-Herxheimer reaction; NN: newborn; STI: sexually transmitted infections; MIU: million international units.*

population:

BPG as above, informing her of the possibility of a non-severe skin reaction

2) Low to intermediate risk situations and intermediate risk situations:

- Tolerance induction **in hospital, under medical supervision, before each BPG injection**[2]
- OR ceftriaxone 1 g daily IM or IV for 14 days (early or late syphilis) with hospital monitoring of the injections during the first two days of treatment

3) Situations at high risk of an immediate severe reaction: skin tests should be performed rapidly to prevent delay of maternal treatment. If skin tests cannot be performed within a few days, multidisciplinary consultation should be set up quickly (allergy specialist, obstetrician, pediatrician).

4) Situations **at high risk of delayed severe allergic reaction:** doxycycline PO 100 mg × 2/d for 14 days (early syphilis) or 21 days (late syphilis).

Treatment should be instituted as early as possible and ideally completed before 16 weeks' gestation.

Treatment must be restarted from the first dose if an interval of more than nine days elapses between two doses of BPG (regardless of stage) and interruption of more than 24 h for benzylpenicillin IV.

Related measures:

- **Prevention of IM-related pain**: replace 0.5 to 1 mL of solvent with non-adrenalized lidocaine 1 %**.**
- **Prevention and management of JH reaction**: (1) inform women of any adverse effects that may occur (fever, uterine contractions, decrease in active fetal movements) and that they should consult immediately if necessary; (2) offer acetaminophen PO 1 g 2 h before BPG injection, then 1 g/ 8 h for 72 h and, alternatively or in combination, in the event of fever above 38 °C for more than two hours, prednisone 0.3 to 0.5 mg/kg/day PO for 48 h (not to exceed 60 mg per day).

5.4. *Treatment-related measures*

5.4.1. *Checking for other STIs*

Data for pregnant women are scarce. A recent US retrospective study of 73 pregnant women with a diagnosis of syphilis reported a frequency of co-infection with HIV of 1.2 %, with *Neisseria gonorrhoeae* of 8.2 %, with *Chlamydia trachomatis* of 9.6 %, and with hepatitis B of 1.4 % [121]. When diagnosing syphilis, international guidelines suggest systematic screening for HIV [15,28] and hepatitis B and C [28]. In France, screening for *C. trachomatis* and *N. gonorrhoeae* may be proposed [45].

5.4.2. *Screening of sexual partner(s)*

The benefit of screening the woman's sexual partners is that it enables their treatment, thereby preventing the cycle of reinfection. Failure to screen partners is associated with an increased risk of adverse outcome for the child [122]. The French *Société de Dermatologie* recommends clinical examination, serologic screening, and/or treatment of sexual partners, depending on the duration of maternal syphilis and the date of her last unprotected sexual intercourse. In the case of early syphilis, it recommends systematic treatment of partners with the most recent contact less than six weeks before her diagnosis, serologic screening of partners with the most recent contact more than six weeks previously, and the treatment of positive partners [55].

[2] https://www.cnr-ist.fr/documents-de-reference-2.html.

5.4.3. *Preventive measures to avoid contamination of sexual partners*

After penicillin is administered, while the presence of *T. pallidum* DNA in both ulcerated mucocutaneous lesions and blood can be documented by PCR up to 56 h after the first BPG dose [123], we are lacking in certainty about residual contagiousness past this time. No data are available for other antibiotics.

Some guidelines consider that 24 h after the first dose of BPG, there are no longer any transmissible bacteria. Australian and Canadian guidelines recommend avoiding sexual intercourse without a condom for seven days after BPG treatment; Canadian guidelines also state that it is preferable to wait seven days after the end of non-BPG antibiotic treatment [124,125].

5.4.4. *Precautions and isolation measures for hospitalized patients*

Other persons, particularly hospital staff, are at risk from any unprotected mucocutaneous contact with an unhealed primary or secondary phase rash or mucocutaneous lesion remaining untreated or treated for fewer than seven days, infected secretions, or blood exposure accident during a bacteremic phase [2,11]. No recent data are available about the transmission of syphilis between hospitalized patients or between patients and health care workers.

5.4.5. *Action to be taken by exposed health care personnel*

There are no specific recommendations in this situation. In the event of high-risk contact, i.e., unprotected contact with a mucocutaneous lesion or an unhealed primary or secondary phase contagious rash, infected secretions, or a blood exposure accident during a potentially bacteremic phase, treatment of the exposed person has been shown to reduce the risk of syphilis [1]. By analogy with the general population, the treatment of an exposed health care worker recommended by learned societies consists in administration of a single dose of 2.4 million IU of BPG IM [1,55].

RECOMMENDATION 6: What are the measures associated with maternal treatment?

(Fig. 4**).**

- **Inform the patient of the importance of screening and treating her partners (risk of reinfection). Sexual abstinence until at least seven days after completion of a full course of treatment AND healing of contagious lesions AND full treatment of partners**
- **No reason to delay pregnancy beyond seven days after completion of a full course of treatment**

5.5. *Maternal monitoring in the event of syphilis during pregnancy*

Surveillance is based on NTT monitoring that uses the same technique and preferably the same laboratory, due to the variability of these tests [1,57]. There are no data on the specific course of NTT titers in pregnant women.

The course of the NTT titer depends on the syphilis stage:

Early syphilis.

In the general population, a favorable response under treatment is defined by a division of the NTT titer by four, corresponding to a decrease of two dilutions, at three months of treatment. It is observed in over 75 % of patients [85]. Negative NTT confirms cure [2,57]. However, at one year after treatment, NTT remains positive in 15 %–41 % of patients [126,127]. NTT that rises by a factor of four strongly suggests reinfection.

Late syphilis.

NTT decay is slower [1,127]. In a historical cohort of 128 patients having undergone treatment for late latent syphilis, only 44 % were NTT-negative five years after treatment, with residual titers below 64 and mainly between four and eight [128]. According to available data, NTT findings more slowly become negative in cases of uncontrolled HIV co-infection [1].

The recommended frequency of monitoring differs for the general population and pregnant women. Some professional societies recommend that the frequency of NTT testing be increased so as to adapt management at an early stage [15,45,125]. In the case of (early or late) infection diagnosed before 24 weeks' gestation, the CDC recommends NTT testing at two months after treatment and at delivery. In the case of infection diagnosed after 24 weeks' gestation, the CDC recommends monitoring only at delivery [15]. Canadian guidelines call for NTT monitoring at one, three, six and 12 months of treatment after the end of treatment for early syphilis, and at 12 and 24 months for late syphilis [53]. Because monitoring must also take into account the risk of maternal reinfection [56], some professional societies recommend monthly follow-up in situations at high risk of reinfection [53].

RECOMMENDATION 7: When is maternal surveillance during pregnancy to be carried out?

(Fig. 4**).**

- **One-month consultation: check that adequate treatment has been carried out, screen for other STIs, assess the risk of reinfection (ask the patient about screening and treatment of partner(s)).**
- **Check NTT at two months, then once a month until delivery.**
- **NTT in all cases at delivery (for comparison with neonatal peripheral blood NTT)**
- **After delivery, check NTT at three, six, and 12 months after completion of treatment and at 24 months for late syphilis.**
- **Should NTT rise again, suspect treatment failure or reinfection, and seek specialist advice.**

Follow-up of NTT, if possible with the same test (RPR or VDRL) and in the same laboratory. TT titer monitoring is not recommended.

5.6. Fetal monitoring for congenital syphilis during pregnancy

5.6.1. Ultrasound signs (Table 3)

Prenatal screening for CS is based on ultrasound. Canadian and English learned societies suggest the value of targeted ultrasound to search for signs of fetal infection, but do not specify how often they should take place [53,56].

The main ultrasound signs of fetal damage are thickened placenta, hepatosplenomegaly, anemia, subcutaneous edema, hydramnios, hydrops, hyperechoic bowel, and fetal growth restriction without comparison to a reference cohort [112,129–131]. These signs can appear as early as 18 weeks' gestation [117]. They are not specific. The presence of ultrasound signs is associated with an increased risk of unfavorable fetal and neonatal outcomes (e.g., prematurity, CS) [112,129]. Moreover, the absence of sonographic signs does not rule out the possibility of fetal damage. In a study of 32 children with CS, 12 % had normal prenatal ultrasound before maternal treatment [129]. It is possible that the ultrasound performance reported in this study does not reflect how repeated targeted ultrasound by a trained operator is performed.

Several case reports have described the disappearance of ultrasound signs after maternal treatment. Hydramnios, ascites, and fetal anemia are the first to disappear, with thickened placenta and hepatomegaly resolving secondarily [119,129]. The disappearance of ultrasound signs after treatment does not confirm either fetal recovery or absence of CS [129].

5.6.2. Diagnostics

Confirmation of fetal infection is based on detection of *T. pallidum* in amniotic fluid [112]. It can be performed by dark-field microscopy, which has sensitivity of 42 %–86 % and limited availability, or by PCR with sensitivity of 75 %–100 % [117]. Fetal blood sampling for liver function tests [112], PCR on fetal blood [80], and fetal serology have also been described [112]. No learned society recommends amniocentesis or fetal blood sampling for maternal syphilis.

5.7. Management of syphilis during labor and delivery

Maternal serology at delivery.

Some guidelines mention that when syphilis has been diagnosed and treated during pregnancy, NTT assay may be valuable at delivery to assess the risk of CS and reinfection. The delay between treatment and delivery does not always allow the expected NTT titer to be divided by at least 4 [15,56,132].

Delivery route.

The risk of transmission of primary syphilis involves both hematogenous passage and contact with the chancre as it passes through the genital tract [2,11].The literature is devoid of data evaluating the benefit of cesarean delivery in reducing the risk of maternal-fetal transmission in cases of contagious genital mucocutaneous lesions. No recommendations address this issue.

5.8. Postpartum care

There are no specific recommendation for the management of syphilis diagnosed during or *after* childbirth.

No transmission through breast milk has been reported. Most guidelines do not address the subject of breastfeeding. Some experts consider that contagious breast lesions or rashes are contraindications to breastfeeding [133–135].

Postpartum therapeutic education improves follow-up and promotes comprehensive treatment [136].

RECOMMENDATION 8: Fetal monitoring for syphilis during pregnancy (Fig. 4**).**

Do not delay treatment to perform fetal monitoring.

When syphilis has been properly treated before 16 weeks' gestation, perform standard fetal ultrasound monitoring.

In other situations:

- **Initially evaluate the fetus when** the maternal infection is diagnosed, using ultrasound to look for signs of CS (Table 3).
- Consider **referral to a multidisciplinary center for prenatal diagnosis** and appropriate obstetric follow-up.
- **Amniocentesis may be discussed if** an ultrasound abnormality is observed, to investigate differential diagnoses and test amniotic fluid for *T. pallidum* by PCR. A positive PCR confirms the diagnosis of fetal infection, but a negative PCR does not rule it out. Amniocentesis is not recommended in the absence of suggestive ultrasound findings. Fetal blood sampling is not recommended.
- A prenatal **pediatric consultation** should be offered.

The disappearance of sonographic signs after maternal treatment suggests — but does not confirm — fetal recovery. The absence of sonographic signs does not rule out CS.

RECOMMENDATION 9: How to manage maternal syphilis during labor and delivery?

Preventive measures to avoid maternal-fetal transmission intrapartum.

- **If syphilis has been adequately treated during pregnancy,** NTT assay should be performed at delivery. Remaining management is as usual: vaginal delivery, scalp sampling during labor, and instrumental delivery are permitted.
- **The presence of active syphilis lesions or the presence of untreated or inadequately treated syphilis during labor is not an indication for cesarean section.**
- **If maternal care was inadequate** before delivery, adequate care must be provided without delay during the postpartum period**.**
- **If an ulcerated genital lesion is discovered during delivery,** look for syphilitic or herpetic infection.

Assessment at delivery (Table 4).

- **Perform maternal NTT** at delivery for comparison with neonatal NTT
- **In situations where the risk of CS is high or intermediate, the following additional diagnostic tests can be conducted if readily available:** *T. pallidum* DNA test of placenta, immunohistochemical examination of placenta, PCR of cord blood, etc.

Postpartum and breastfeeding.

- **Breastfeeding is not contraindicated.** Infectious disease specialist advice is necessary if a primary or secondary breast lesion is found in a breast-feeding woman.
- **Inform women about STI prevention methods and the continued need for partner screening.**

6. Congenital syphilis

6.1. Risk factors for congenital syphilis

The risk factors identified in several studies and confirmed in recent *meta*-analyses [30,108] are:

— **An early stage of maternal syphilis** (adjusted odds ratio 21.6, 95 % CI 2.10–221.4) [113].

— **High maternal NTT titer at diagnosis**: The risk of CS correlates with maternal NTT titer [137] and increases significantly when NTT ≥ 8, according to a *meta*-analysis compiling eight studies and 1161 patients [138].

— **Inadequate maternal treatment:** Numerous studies of NTT-positive mothers have shown a high risk of CS in children of mothers having received incomplete treatment [77] or treatment not based on BPG [109] or no treatment at all [109,138].

— **Gestational age at the time of maternal treatment:** Several studies have reported a higher risk of CS in NTT-positive mothers when treatment begins after 28 weeks' gestation or is completed fewer than four weeks before delivery. In a Chinese comparative study of 5770 pregnancies, the risk of CS was significantly higher when maternal treatment began at or after, compared with before, 28 weeks' gestation (CS, OR 8.06, 95 % CI 2.93–22.2) [109], with the risks probably a continuum [139]. A literature review of seven recent studies estimates the efficacy of maternal treatment in preventing CS at 95 %-98 % when correctly administered before 28 weeks [108]. Another comparative study of 417 pregnancies found that patients with treatment completed less than four weeks before delivery had a higher risk of CS than those whose treatment was completed more than four weeks before birth (CS defined by darkfield microscopy or an immunofluorescence-positive specimen, clinical features compatible with CS and NTT four times that of the mother, positive IgM or positive NTT at 18 months) (adjusted OR 11.93 (CI95 3.82–37.28) [113]. The possibility of transplacental passage has been documented from 16 weeks' gestation in *ex vivo* and *in vivo* data [140]. The rare case reports of children with CS born to mothers treated before 15 weeks [137,138] did not rule out maternal reinfection as the cause of CS.

At the end of the pregnancy, and depending on the risk factors mentioned above, learned societies classify situations into different risk levels for CS.

Guidelines identify the following situations as at **high risk of CS:**

- Mother did not receive treatment or it was incomplete [15,50,56,141]
- Maternal treatment did not include penicillin [15,50,141] or beta lactam [56].
- Maternal treatment was completed fewer than 30 days before delivery [15,56,141].
- NTT decreased less than 4-fold after maternal treatment [15,50,56].

They also cite the stage of maternal syphilis at diagnosis as another identified risk factor, but it was not included in the gradation of risk [56,141].

They all classify the situation of a mother treated before pregnancy and with no evidence of reinfection during this pregnancy as being **at zero risk of CS**. No case of CS has been described in women whose positive TT was associated with negative NTT [142].

Learned societies do not mention the case of a pregnant woman with full completion of treatment before 16 WG.

Other situations are classified as "**low risk**" or "**intermediate risk**" according to **CS** guidelines**.**

6.2. Diagnosis in neonates

CS can be early-onset (< 2 years) or late-onset (≥ 2 years), with specific clinical signs in each case. Diagnosis of CS is difficult. Some tools can be used to confirm the diagnosis at birth, but none to rule it out. The diagnosis is based on a combination of history (risk factors) and clinical and laboratory test findings.

6.2.1. Clinical examination of the newborn at birth

In most cases, signs of early CS are not visible at birth but appear within the first four weeks of life. A normal clinical examination at birth therefore does not rule out CS [24,143]. CS appears to be more severe in children born preterm [24].

Table 4
Syphilis checklist for the delivery room.

Item	What to do
For patients diagnosed with syphilis during pregnancy	
Information on CS risk level recorded in the obstetric record (high, intermediate, or nil) • Date of end of maternal treatment • Antibiotic administered • Stage of maternal infection • NTT update if available	**High risk** Early maternal syphilis (< 1 year) after 16 weeks' gestation OR initial maternal NTT titer > 8 after 16 weeks OR maternal treatment not received or incomplete OR maternal treatment without penicillin G OR maternal treatment initiated after 28 weeks OR maternal treatment completed < one month before delivery OR no decrease in maternal TNT by a factor of four after 2–3 months of treatment (if ≥ 4 at diagnosis) **No risk** Maternal syphilis adequately treated < 16 days' gestation, with serological decline, and no evidence of reinfection **Intermediate risk** Other cases
Adherence to standard precautions and asepsis rules during delivery and care of newborn babies	Standard precautions Contact precautions if contact with mucous membranes or contagious skin lesions
Clinical examination of the newborn	Look for signs of CS, follow additional contact precautions Any nasal discharge or lesion may be sampled for PCR
Mother and child serum sampling (peripheral blood)	Comparison of children's and mothers' NTT titers Anti-treponemal IgM assay for children, if available
For patients with a high or intermediate risk of congenital syphilis for their child	
Take placenta fragment for PCR and IHC if available at the facility	

CS: congenital syphilis; NTT: nontreponemal test; IHC: immunohistochemistry.

6.2.2. Examination of the placenta

Macroscopic examination of the placenta may reveal thickened placenta (56.8 %), which is nonspecific [144]. Most learned societies recommend histologic examination of the placenta [15,50,56,145], as it increases the probability of identifying CS when used in addition to clinical, radiologic, and laboratory assessments. This probability rose from 67 % to 89 % in a study of 33 neonates of infected mothers [146]. It may reveal lesions of acute funiculitis or villitis, which are inconsistent and nonspecific [144,146].

International guidelines agree that the diagnosis of CS is **proven** when *T. pallidum* DNA is detected in the placenta [15,50,56,145]. PCR, however, lacks sensitivity. In an analysis of 215 placentas with CS by Marais et al. [144], PCR had sensitivity of 25.8 %, while that of immunohistochemistry (IHC) was 74.4 %. The combination of these two methods led to the identification of 42 cases of CS for which serology alone was noncontributory (negative or unknown). A negative test (PCR or IHC) does not rule out the diagnosis of CS.

6.2.3. Serologic examination of the newborn from peripheral blood

Peripheral blood serology is the basis for diagnosis, but due to the transplacental passage of maternal IgG, it is difficult to interpret before six months of age,.

Available recommendations suggest that maternal and neonatal blood samples be taken concomitantly, between birth and the second or third day afterward, for **comparative analysis of their serology** [147,148].

Due to a theoretical risk that they may be contaminated by maternal blood, **neonatal samples should not be taken from cord blood**,.

Treponemal tests.

Detection of treponemal IgG in a newborn does not allow us to distinguish between two situations: either passively transmitted maternal antibodies, which may persist for up to 18 months of life, or antibodies in the child reflecting CS [149]. International recommendations systematically suggest testing newborns in the first few days of life [15,56,141], to monitor possible serologic decline. Negative TT at 18 months of age rules out CS [149]. Unlike IgG, maternal IgM does not cross the placenta. Detection of treponemal IgM in neonates is therefore specific for CS, but its sensitivity is inconsistent, particularly:

- In cases of early fetal infection (IgM disappears before birth)
- OR if fetal infection occurs very late in pregnancy [150],
- OR in a neonate with early CS but still asymptomatic. In a study of 101 neonates at risk of CS, Bromberg et al. [147] reported sensitivity of 14 % for the detection of specific IgM by Western blot in asymptomatic newborns (1/7) and 100 % in newborns with CS symptoms (12/12). Similarly, among 116 newborns at risk of CS, Stoll et al. found sensitivity of 7 % in asymptomatic infants and sensitivity and specificity of 88 % and 97 % respectively in the 18 who were symptomatic [151].

European guidelines systematically call for a neonatal plasma-specific IgM assay, and its simple presence classifies the risk of CS as "probable", whereas British guidelines consider its presence sufficient to confirm the diagnosis [56]. The CDC and WHO do not recommend this assay [15,141].

Nontreponemal tests.

The detection of NTT in children reflects either CS or maternal Ig transmission. In the case of passive transfer, NTT results should decrease and become negative by six months of age.

Positive NTT in a neonate with a titer at least four times higher than that of the mother is highly suggestive of immunoglobulin neosynthesis by the child, and consequently very likely to be CS [149]. Some authors suggest that this high ratio is in favor of CS that is already symptomatic at the time of sampling [147,149]. The reported sensitivity of a neonatal/maternal NTT ratio $\geq$ 4 is very low (4–13 %) [147,149], as it may be underestimated when the maternal NTT titer is high, or maternal syphilis was acquired shortly before birth, or birth occurred before the constitution of an effective fetal humoral response [147].

Available recommendations suggest that a blood NTT assay should be performed systematically in newborns and that they should be considered infected if the neonatal/maternal NTT ratio is $\geq$ 4 [15,50]. However, absence of this isolated criterion does not rule out the diagnosis. European and British guidelines suggest a systematic check of neonatal NTT at three months of age, and a follow-up to ensure that it has become or remains negative at six months of age.

6.2.4. Testing for t. Pallidum in neonates by PCR of cord blood or nasopharyngeal secretions

The available studies and the resulting recommendations agree on the poor sensitivity and good positive predictive value of specific PCR for the diagnosis of CS. None of the guidelines include it in the list of tests to be carried out systematically to detect CS.

The few available data (from the series by Tsang et al. [152]) estimate sensitivity for cord blood at 7.8 % (4/51). Most guidelines from international learned societies [15,50,56,145] mention that this test can be performed on cord blood, without formally recommending it take place.

The sensitivity of nasopharyngeal secretions was 15.7 % (8/51) in the series by Tsang et al. [152].

6.2.5. CSF examination for the diagnosis of congenital syphilis

A study of 148 children showed that the low sensitivity of VDRL (53 %), pleocytosis (38 %), and elevated protein content (56 %) in CSF makes its examination of little use in the diagnosis of CS [153]. Similarly, in a *meta*-analysis combining three studies and 217 patients *T. pallidum*, DNA testing of CSF by PCR demonstrated low sensitivity (62 %) [154]. In a study of 1070 asymptomatic newborns, CSF cytology and biochemistry did not differ between children at low and high risk of CS [155]. Moreover, the cellularity and protein content of newborns' CSF depend on term at birth and actual age and are therefore to be interpreted according to the available charts.

6.2.6. X-ray examinations

X-rays of the long bones have been described as of little use for the diagnosis of CS alone in asymptomatic newborns, as they are never abnormal in isolation [156] and are associated with a neonatal/maternal NTT ratio $\geq$ 4 [24].

6.3. Confirming the diagnosis of congenital syphilis

Early congenital syphilis.

The criteria for certainty of a CS diagnosis vary among the professional societies that have considered the question, with the following considered as sufficiently robust:

- Clinical signs of early CS: alone for some guidelines [15], or together with positive TT from an infant peripheral blood sample for others [50,56,141].
- OR neonatal/maternal peripheral blood NTT ratio $\geq$ 4 at birth.
- OR detection of *T. pallidum* DNA in any placental or infant specimen [50,56].
- OR detection of neonatal treponemal IgM [50,56].
- Some have combined this with the detection of *T. pallidum* by placental IHC [50,141].

Late congenital syphilis.

All of the experts cited here consider this diagnosis proven in children with clinical signs of late CS and positive syphilis serology after the age of 24 months (TT + NTT). They also remind us that any positive syphilis serology in a child should be followed by a search for clinical signs of late CS, and/or evidence of sexual abuse.

Learned societies recommend that laboratory tests be conducted as

soon as the diagnosis is suspected [15,50] or as part of the work-up of infected children [56].

These investigations vary according to the level of CS risk.

In situations characterized by a high risk of CS, there is a consensus that the following tests be performed:

- Liver function tests, serum ionogram (electrolyte panel), serum creatinine,
- Urine dipstick for proteinuria testing
- Complete blood count, platelet count
- CSF puncture for cytologic examination, measurement of proteins, and search for intrathecal antibody secretion (VDRL)
- X-rays of long bones
- Complete ophthalmologic examination [50,56]

These guidelines vary for "low-risk" or "intermediate-risk" situations in asymptomatic children. The British do not perform the full extensive work-up described above [56].

RECOMMENDATION 10: How to assess the risk of congenital syphilis at birth by maternal status? (Fig. 5).

Three levels of risk for neonatal infection have been defined:

1) High risk of CS:

- Early maternal syphilis (primary, secondary or latent for less than one year) after 16 weeks' gestation
- Initial maternal NTT titer ≥ 8 after 16 weeks
- Maternal treatment not received or incomplete
- Maternal treatment without penicillin G
- Maternal treatment initiated after 28 weeks
- Maternal treatment completed less than four weeks before delivery
- Absence of 4-fold decrease in maternal NTT after three months of treatment (if ≥ 4 at diagnosis)

2) Zero risk of CS: complete maternal treatment with BPG before 16 weeks' gestation in the absence of any suspicion of maternal reinfection and with none of the high-risk criteria above.

3) Intermediate CS risk: all other situations.

RECOMMENDATION 11: How to diagnose congenital syphilis in newborns?

(Fig. 5).

— **Examine any neonate with a diagnosis of maternal syphilis for signs of CS** *(from birth for all children at high or intermediate risk of CS).*

— **Take a blood sample as soon as possible after birth** (at the latest within 3 days after birth) from **any newborn whose mother had positive syphilis serology during pregnancy** (excluding serologic scars) **to perform TT and maternal and neonatal NTT on peripheral blood** sent to the same laboratory **for calculation of the newborn/maternal NTT ratio and for IgM testing by immunoblot on neonatal peripheral blood**.

These tests will be performed even in newborns assessed "zero risk" to verify the absence of maternal reinfection.

— **If there is a high risk of CS, obtain the result of the neonatal/maternal NNT ratio before the child is discharged from hospital**.

— **In situations with a high or intermediate risk of CS, the following additional tests may be performed if they are readily available**: *T. pallidum* DNA testing of placental samples, immunohistochemical examination of placenta, PCR of cord blood and other secretions.

RECOMMENDATION 12: Assessing the diagnosis of congenital syphilis?

Four levels of congenital syphilis probability are defined:

- **Proven or probable CS:** fetus or child with
  - Clinical signs of CS and mother had syphilis infection during pregnancy
  - OR neonatal/maternal peripheral blood NTT ratio ≥ 4 at birth
  - OR detection of *T. pallidum* by PCR on any placental or biologic sample from the fetus or child (proven)
  - OR detection of *T. pallidum* by placental IHC (proven)

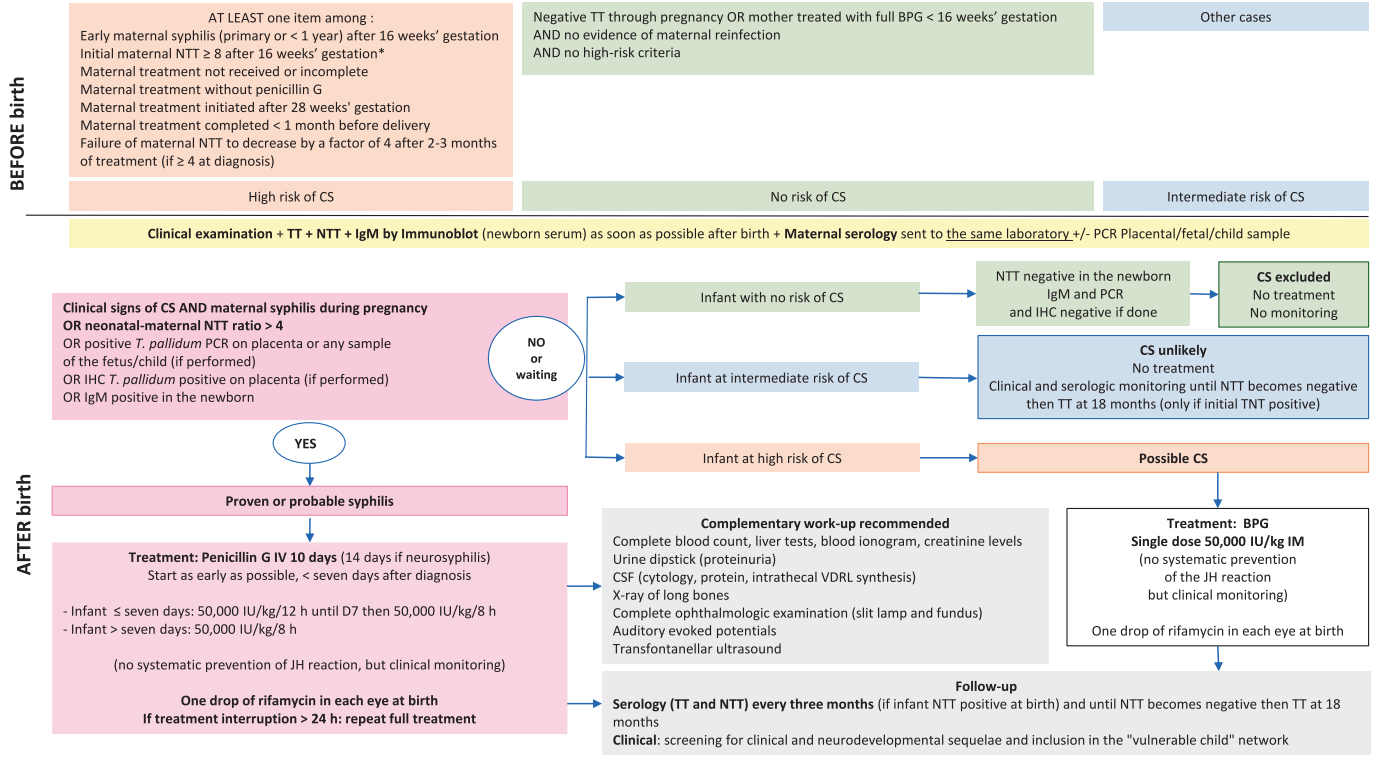


Fig. 5. Classification and postnatal management of congenital syphilis. *BPG: benzathine penicillin G; CS: congenital syphilis; M: month; JH: Jarisch-Herxheimer reaction; IHC: immunohistochemistry; NTT: nontreponemic test; IM: intramuscular; VDRL; Venereal Disease Research Laboratory test.*

- OR neonatal plasma IgM positive
- **Possible CS**: newborn at high risk of CS AND previous criteria absent
- **Unlikely CS**: newborn at intermediate risk of CS AND criteria for proven/probable CS absent
- **CS excluded:** newborn whose mother received full treatment with penicillin G before 16 weeks' gestation

RECOMMENDATION 13: How to evaluate congenital syphilis.

The following tests are recommended in cases of proven or probable CS:

- Complete blood count
- Liver function tests, serum ionogram (electrolyte panel), serum creatinine
- Urine dipstick for proteinuria testing
- CSF puncture for cytologic examination, measurement of proteins, and search for intrathecal antibody secretion (VDRL)
- X-rays of long bones
- Complete ophthalmologic examination with slit lamp and fundus examination
- Auditory evoked potentials
- Transfontanellar ultrasound.

It is recommended that these explorations not be performed except in these situations.

6.4. Neonatal management

Therapeutic indications are broad. No clinical trials have assessed the treatment of definite CS. Initial guidelines are based on expert opinion, extrapolated from those for adult neurosyphilis, supplemented by a few case reports and neonatal pharmacokinetic studies. Only two small randomized controlled trials have tested treatment of neonates at risk of CS.

6.4.1. Substances studied

Benzylpenicillin IV or IM.

In 1994, in a prospective study of 163 CSF samples from infants with certain or probable CS, Azimi et al. first demonstrated its diffusion in the CSF of neonates [157]. Among the 23 neonates treated with benzylpenicillin at a dose of 50 U/kg/12 h and 40 neonates treated at a dose of 100 U/kg/12 h for 10–14 days, 100 % of the assays performed between injection and H12 were above the minimum effective concentration.

Benzathine Penicillin G.

Its concentration falls rapidly in CSF, reaching subtherapeutic levels 48 h after injection in two studies involving 4 and 60 neonates, respectively [158,159], despite satisfactory concentrations in serum.

Ceftriaxone.

This drug has not been studied for CS. It is proposed in the UK guidelines for outpatient treatment.

There are no data on antibiotic treatment with azithromycin or doxycycline in penicillin-allergic children with CS.

6.4.2. Treatment duration

Optimal duration has not been studied, but has been extrapolated from that recommended for adult neurosyphilis [160], i.e., 10–14 days [50]. If treatment is interrupted for more than 24 h, the complete regimen should be repeated [161].

6.4.3. Treatment by risk level

Two randomized controlled trials have evaluated the treatment of asymptomatic infants at risk of CS:

Intermediate risk (inadequate maternal treatment during pregnancy).

Paryani et al. compared a single dose of BPG (50,000 U/kg) to procaine penicillin (50,000 U/kg/d for 10 days) in 152 asymptomatic newborns: no clinical CS occurred in either arm (0/68 and 0/84 [162].

High risk (maternal syphilis with NTT (VDRL/RPR) ≥ 32 at delivery, no maternal treatment, and normal CSF features and bone X-rays).

Radcliffe et al. compared patients with a single dose of BPG (50,000 U/kg, n = 12) to those receiving therapeutic abstention (n = 10). The study was stopped early due to an increased risk of CS in the untreated group. No failure at 24 weeks after birth was identified among the 12 infants treated, including the two with specific IgM at birth. The small number of patients and the absence of long-term follow-up provide an insufficient level of evidence to draw conclusions on the efficacy of BPG in neonates at high risk of CS [163].

6.4.4. Prevention and management of Jarisch-Herxheimer reaction

A retrospective study published in 2017 reported a Jarisch-Herxheimer (JH) reaction in 18 % of 60 newborns treated for CS. Risk factors were bone involvement, multiorgan involvement and high NTT (≥ 256). Clinical manifestations of this reaction were fever, polypnea, tachycardia, irritability, and worsening of preexisting skin lesions [164]. These manifestations have also been described in other publications [165]. Treatment of this reaction was based on dexamethasone 0.1–0.3 mg/kg IV, with no interruption of antibiotic therapy. The course was favorable in all cases.

JH reaction and its prevention in newborns are not addressed in the available recommendations.

6.4.5. Indications for treatment in the neonatal period according to available guidelines

- In cases of probable CS, i.e., where there is a high risk of CS but no "proven" CS criterion, the guidelines all agree on the administration of a treatment, which varies from a single dose of BPG to a 10-day IV course of benzylpenicillin [15,50,56,141].
- In cases of possible CS, i.e. where there is a low risk of CS and the criteria for "proven" CS are not met, US guidelines suggest a single dose of BPG, while UK guidelines suggest clinical and laboratory monitoring of neonates without treatment, while European guidelines are silent.
- No risk of CS: guidelines suggest no treatment.
- Any late-onset CS (> 24 months) warrants management (further investigations, treatment, follow-up) in the same way as early-onset CS in all available guidelines [15,50,56,141].
- Associated prophylaxis of neonatal conjunctival infections: In the context of maternal syphilis, the 2016 AFSSAPS recommendations recommend Rifamycin eye drops for the prevention of sexually transmitted conjunctivitis (one drop in each eye at birth) [166].

RECOMMENDATION 14: How to treat congenital syphilis in newborns? (Fig. 5).

Start treatment as early as possible (certain or probable CS), and in all cases within 7 days of diagnosis.

— **Proven** or **probable CS**.

– newborns ≤ 7 days: benzylpenicillin IV, 50,000 IU/kg/12 h up to 7 days and then 50,000 IU/kg/8 h for a total of 10 days or 14 days (neurosyphilis).

– newborns > 7 days: benzylpenicillin IV 50,000 IU/kg/8 h for 10 days or 14 days (neurosyphilis).

– Late-onset CS (> 2 years): same treatment as early-onset CS.

— **Possible CS**: One dose of BPG 50,000 IU/kg/dose IM. The addition of xylocaine is contraindicated.

— **Unlikely or excluded CS**: **no treatment**.

In all cases:

— **One** drop **of rifamycin in each eye at birth for the prophylaxis of conjunctival infections in** each **neonate**.

— **If treatment is interrupted > 24 h, repeat a full course of treatment.**

— **Advice from ID specialists may be sought in cases of atypical involvement**

— **No systematic preventive treatment of JH reaction is recommended,** but clinical monitoring should be carried out, particularly in infants at the highest risk (bone involvement or involvement of at least 3 organs or high NTT $\geq$ 256). In the event of symptoms suggestive of a JH reaction, administer a dose of dexamethasone (0.1—0.3 mg/kg) IV without interrupting antibiotic therapy.

— **Breastfeeding is not contraindicated**

6.5. Child follow-up

All guidelines call for clinical and serologic follow-up every three months until NTT negativation**,** to ensure the absence of infection, even if this follow-up is described as difficult, with many patients lost to follow-up (65 % at 6 months [117]).

An absence of infection is defined in these guidelines [15,56] as:

- Negative NTT no later than six months of age.
- TT results with descending kinetics, and negative no later than 18 months of age

A definite or probable infection warrants regular neurodevelopmental monitoring.

A new rise in NTT during follow-up indicates late infection, relapse, or reinfection, and justifies an extensive workup and the initiation of emergency treatment, according to guidelines that address this point [15,56].

RECOMMENDATION 15: What are the follow-up procedures for congenital syphilis in newborns?

- **Follow-up clinical and serological tests (TT and NTT) every 3 months for any neonates with a positive NTT at birth.** This follow-up should be continued until NTT has become negative.
- **Order a serology test at 18 months, to ensure the disappearance of TT if positive at birth**
- **Cure can be confirmed by negative NTT**.

A rise in NTT (after treatment or in the absence of treatment) indicates late infection, relapse, or reinfection and warrants clinical reassessment, further investigations, and urgent treatment**.**

- **In case of proven or probable CS:**

Offer specific pediatric follow-up for early detection and guidance about possible clinical and neurodevelopmental sequelae in the "vulnerable child" network.

- **In case of unlikely or excluded CS, it is not recommended to follow up an infant with negative NTT at birth.**
- **In the event of initial CSF damage, a follow-up LP is not recommended.**

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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