Pediatr Infect Dis J, 1991;10:516–22
0891-3668/91/$03.00/0

Vol. 10, No. 7
Printed in U.S.A.

CENTERS FOR DISEASE CONTROL: CURRENT ISSUES IN PEDIATRICS. EDITED BY WALTER ORENSTEIN, M.D.

Congenital syphilis: trends and recommendations for evaluation and management

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The Centers for Disease Control (CDC) recently changed its recommendations for reporting,[1] managing and treating[2] infants with congenital syphilis. In this article we review these changes, discuss their rationale and propose an algorithm for carrying out these recommendations.

HOW MANY CASES OF CONGENITAL SYPHILIS ARE THERE?

The number of cases of congenital syphilis reported to CDC has been increasing since 1985, following an ongoing increase in cases of early syphilis in women (Fig. 1).[3] For 1990, 2841 cases of congenital syphilis were reported among infants younger than 1 year of age. In contrast only 688 cases were reported in 1988, which was then the highest total since the early 1950s, when penicillin was first widely used to treat syphilis. The difference reflects not only increased maternal syphilis but also a new surveillance case definition.

Before 1989 only infants who had clinically apparent disease or laboratory findings suggestive of congenital syphilis had been consistently reported to CDC. Although at least half of infected liveborn infants have no signs of congenital syphilis at birth,[4–6] they were often not reported even though they usually receive presumptive treatment. Similarly syphilis-associated stillbirths are rarely reported, although up to 40% of pregnancies in women with untreated early syphilis end in perinatal death.[4, 7, 8] Besides being underreported congenital syphilis was inconsistently reported. Case definitions of congenital syphilis have been complicated, and interpretations of criteria for reporting cases have not been consistent across states or over time.[9]

In response a new surveillance case definition for congenital syphilis was recently approved by the Council of State and Territorial Epidemiologists and CDC.[10] This case definition should improve surveillance by simplifying and standardizing reporting of congenital syphilis by public health jurisdictions; it calls for reporting all infants (and stillbirths) born to women with untreated or inadequately treated syphilis at delivery, regardless of neonatal symptoms or findings. This definition was used in 1989 by New York City, and in 1990 by many of the states that usually report the largest numbers of cases of congenital syphilis. Most other states and reporting areas will implement the new definition in 1991.

The large increase in the number of cases of congenital syphilis between 1988 and 1990 was therefore expected. A study in Los Angeles demonstrated that if all the infants who received presumptive parenteral therapy 10 days were reported, the total from that county would increase 4- to 5-fold if syphilis-associated stillbirths were included.[11] Other regions also noted similar increases after implementing the new reporting definition.[9] Because the number of cases of early syphilis in women is increasing, however, increases in reported cases of congenital syphilis also reflect greater incidence of disease.

DIAGNOSIS

Although the reporting definition for congenital syphilis has been simplified, the clinical diagnosis is still challenging. Diagnosis in a newborn can be made with confidence in the following situations: (1) positive results are obtained by dark-field microscopy or direct immunofluorescence on specimens from sites such as skin lesions, umbilicus or placenta[12, 13]; or (2) mother has reactive treponemal and nontreponemal tests and the infant manifests classic signs of disease: condyloma lata, snuffles, characteristic skin rashes,

Accepted for publication April 10, 1991.
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Key words: Congenital syphilis management.
Address for reprints: Technical Information Services, Center for Prevention Services, Centers for Disease Control (E06), Atlanta, GA 30333.

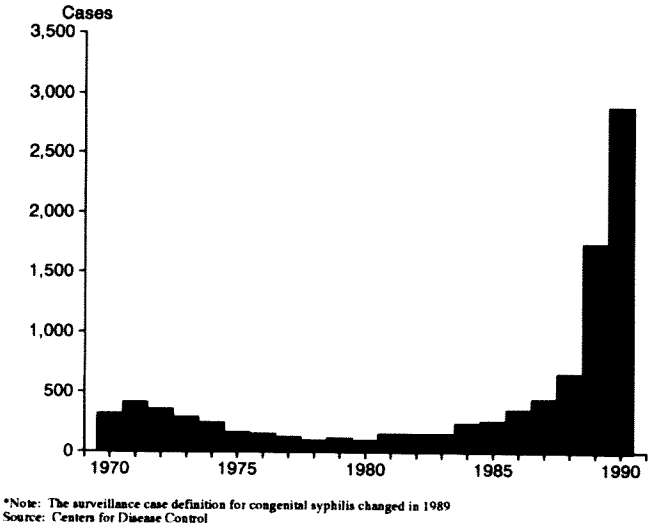

FIG. 1. Cases of congenital syphilis under 1 year of age in the United States.

hepatosplenomegaly, jaundice (syphilitic hepatitis), pseudoparalysis, meningitis or edema (nephrotic syndrome). However, clinicians evaluating newborns at risk for congenital syphilis usually must deal with situations other than these.

The status of syphilis in the mother at delivery, if it can be determined, is very helpful in making the diagnosis of congenital syphilis. If a mother has untreated secondary syphilis, the probability is nearly 100% that her offspring will be infected,[14] permitting a presumptive diagnosis of congenital syphilis. The probability that a pregnant woman with untreated syphilis will transmit infection to her offspring remains high (approximately 70–100%) during the first 4 years after acquisition[4-6, 15] and then decreases.[4, 5]

However, often it is not possible to determine how long the mother has been infected or even if she has active infection; frequently she has a positive but low titer on a nontreponemal test and a vague, undocumented history of treatment. If her newborn lacks the clinical or microscopic evidence of syphilis, described above, the diagnosis of congenital syphilis is difficult and must be based on a combination of clinical signs, laboratory tests and follow-up serologic tests obtained during the first year of life.[16] The decision to treat, however, usually must be made while the infant is still in the nursery.

Serologic tests for syphilis. Results from serologic tests are usually the basis for the diagnosis of syphilis and are the screening tools for identifying cases of congenital syphilis; CDC recommends that all women be screened at their first prenatal visit and, when living in areas where the incidence of syphilis is high, again during the third trimester and at delivery.[2]

There are two types of serologic tests for syphilis, nontreponemal and treponemal. Nontreponemal tests (e.g. Venereal Disease Research Laboratory (VDRL), rapid plasma reagin (RPR)) measure antibody against a cardiolipin-cholesterol-lecithin complex that is not specific for *Treponema pallidum.* These tests provide quantitative results that tend to correlate with disease activity; therefore, screening should be performed using these tests.

Treponemal tests (e.g. fluorescent treponemal antibody absorption test (FTA-ABS), microhemagglutination assay for antibodies to *T. pallidum)* measure specific antibody to *T. pallidum* and usually remain reactive for life even after successful treatment. Therefore these tests are useful to determine whether a patient ever had syphilis but do not necessarily indicate active infection. Further, because the degree of reactivity does not correlate with disease activity, treponemal test results should be reported only as "reactive," "nonreactive," or "minimally reactive." Test results that are "minimally reactive" (formerly known as 1+) may be false-positive and should be repeated.[17] Treponemal tests are also more expensive and difficult to perform than nontreponemal tests. For these reasons treponemal tests should be limited to confirming positive results from nontreponemal tests, which can yield false positive results in a variety of circumstances: chronic infections other than syphilis; autoimmune diseases[18]; intravenous substance abuse[19, 20]; and perhaps pregnancy. (Whether pregnancy can cause false positive nontreponemal test results is uncertain[21-23]; more commonly seroreactivity reflects current or past, treated syphilis.[21])

False-negative serologic test results also occur, either because the syphilis was recently acquired (seroconversion may not have occurred yet) or because of the prozone phenomenon.[24, 25] The latter occurs when flocculation is inhibited by a high concentration of serum antibody; diluting the serum yields positive test results. Nevertheless a test that has a prozone is not completely negative and should be recognized as such by experienced laboratory technicians.

For several reasons screening tests at delivery should be performed with maternal blood specimens, not cord blood. False positive and false negative results can occur with cord blood specimens.[26] The former are thought to occur because of contamination with Wharton's jelly; the latter presumably occur because infection was acquired late in pregnancy. In this situation a seroreactive mother may deliver an infected infant, seronegative and asymptomatic at birth, who does not become seroreactive until after 1 month of age.[5, 27-29] Furthermore if maternal specimens are obtained at admission for delivery, the test results are available sooner; the use of qualitative RPR tests, which can be performed simply and quickly, may expedite the process. Because no infant should be discharged from the nursery until maternal serologic status is known, this is an important operational issue.[2]

The inability of these tests to rule in or rule out infection in the newborn, given maternal infection, has stimulated research to develop better indicators of congenital syphilis. Research concerning the serologic identification of congenital syphilis is currently focused on IgM. Early studies found that serum IgM was usually increased in infants with congenital syphilis. However, this result was neither specific (it is associated with several other infections and with leak of maternal IgM across the placenta) nor sensitive [6, 30-33] for this disease.

IgM has also been used with other tests, such as the FTA-ABS, performed with anti-IgM, rather than anti-IgG, as the fluorescein-tagged conjugate. However, despite some early success[32, 34] inaccuracies of the test have been documented,[35] and the methodology has been criticized.[36] Among the factors responsible for the inaccuracies were the use of a relatively nonspecific anti-IgM antibody and the presence in the infant of IgG-blocking antibodies and rheumatoid factor.[37] The test has since been improved by the use of purified preparations of anti-IgM antibodies and antigen, which prevents nonspecific binding by rheumatoid factor.[24, 37, 38] Another improvement is the chromatographic separation of patient serum to capture the 19S fraction, thus isolating IgM and eliminating IgG-blocking antibodies. This test, called FTA-ABS-19S-IgM, has performed very well in European trials[39-41] but is labor intensive and at this time is available only in a few United States laboratories, including CDC.

Other IgM-based tests use immunoblotting techniques[42-44] or enzyme immunoassays with IgM capture and either VDRL[45, 46] or treponeme-specific monoclonal antibody.[40, 47, 48] (The latter are used in Europe and are under evaluation in the United States.) All these tests appear relatively unaffected by IgG-blocking antibodies or rheumatoid factor. All have been demonstrated to be accurate in situations in which they are not needed; they are sensitive in identifying congenital syphilis among infants with overt clinical disease and specific in excluding the disease in infants whose mothers definitely do not have syphilis. However, these tests have not been demonstrated to be accurate in the most challenging and frequently encountered circumstance, an infant at risk for congenital syphilis who has a normal evaluation at birth.

A hindrance to the development of the new IgM-based tests is the lack of a reliable standard with which to compare results. *T. pallidum* cannot routinely be cultured, and rabbit inoculation and direct immunofluorescence help in research but are not 100% sensitive. Furthermore IgM-based serological tests have inherent diagnostic limitations. They may yield false positive results at birth because of leakage of maternal IgM across the placenta,[31] and they will not routinely identify an infant whose mother was infected late in pregnancy and has not seroconverted by delivery.[29, 35, 44] Although these may be relatively infrequent events, no perfect diagnostic test for *T. pallidum* yet exists. A solution to this problem may be the polymerase chain reaction being developed for *T. pallidum*. If reliable this test would allow the diagnosis of congenital syphilis to be based on the presence of the organism (i.e. nucleic acids of *T. pallidum)* rather than on the variable antibody response of the host.

Evaluation. Other tests can be used to help determine whether a seropositive infant with a normal physical examination is infected with *T. pallidum*. Radiographs of long bones reveal pathognomonic metaphysial changes in 95% of infants with clinically overt congenital syphilis.[5, 27, 49] (Performed on stillbirths, xeroradiography may be even more sensitive.[50]) The findings in cerebrospinal fluid (CSF) of a positive VDRL or an increase in leukocytes or protein are the hallmarks of neurosyphilis (but see next paragraph). Therefore it is recommended that long bone radiographs and CSF examination be routinely performed among infants evaluated for congenital syphilis.[2] Although these tests are usually abnormal among infants with clinically manifest congenital syphilis, it is not known how useful they are for identifying those infected infants who are normal on examination.

The interpretation of CSF results requires some discussion. To be useful the examination of CSF should yield more information than could be obtained from studies on serum specimens; this is clearly the case when performed among adults. In adults the VDRL, the standard serologic test for use on CSF, is specific although not sensitive for neurosyphilis.[51-53] Conversely the FTA-ABS test on CSF is very sensitive, although not specific.[52-54] (RPR or microhemagglutination assay for antibodies to *T. pallidum* are not reliable tests on CSF and should not be performed[24].) In addition an increased CSF leukocyte count or protein is accepted as indicating central nervous system involvement.

The interpretation of results on CSF specimens from newborns is more difficult because these results are neither sensitive nor specific for neurosyphilis. In newborns some antibodies passively diffuse from serum into the CSF,[55] leading some experts to believe that a positive test on CSF for any antibody reflects only its presence in serum. Similarly CSF leukocyte count $> 5/mm^3$ or protein > 50 mg/dl, abnormal in the adult or child, may be normal findings in the first month of life. Nevertheless despite its lack of specificity, CSF leukocytosis is probably the best marker of active neurosyphilis[5, 15, 56] and, like a reactive CSF VDRL, should not be ignored. On the other hand "normal" CSF results may be misleading: syphilis frequently involves the central nervous system; and a

negative CSF VDRL may reflect antibodies "hidden" in immune complexes.[57]

Because of these considerations the interpretation of results from CSF should vary depending upon the circumstance. When it is likely that the infant is infected, i.e. mother has untreated syphilis, treatment should be provided, regardless of CSF findings. (Evaluation of CSF should still be performed to permit abnormalities to be monitored.) However, when the probability of infection is lower, i.e. mother has an uncertain history of treatment for syphilis and examination of the infant is normal, evaluation of CSF may provide the only evidence of congenital syphilis. CDC recommends that every infant presumed to be infected receive penicillin of sufficient dose and duration to treat neurosyphilis because central nervous system involvement can occur in the absence of CSF abnormalities.

Other results consistent with congenital syphilis include direct hyperbilirubinemia, elevated serum transaminase, Coombs'-negative hemolytic anemia, pneumonia alba (on chest radiograph) and evidence of nephropathy. These abnormalities, typically identified in infants who are symptomatic, are not found as frequently, nor are they as distinctive, as the radiographic findings described above. CDC has not recommended these abnormalities be routinely sought, although some experts obtain liver function tests, urinalysis and chest radiographs on all infants evaluated for congenital syphilis.[58]

PENICILLIN THERAPY FOR CONGENITAL SYPHILIS

Although penicillin was first used to treat congenital syphilis in the 1940s,[59,60] many of the studies on which treatment recommendations have been based are decades old and were not designed to determine the optimal treatment for congenital syphilis. Only one study has ever looked at neurodevelopmental outcome after therapy.[61] However, there is sufficient information about penicillin treatment of congenital syphilis to develop recommendations that reduce the risk of overt treatment failure and define the role of benzathine penicillin G in treatment of congenital syphilis[2].

In 1947 Platou recommended that a total of 100 000 units of aqueous penicillin be given in divided doses every 3 to 6 hours over 12 to 15 days, although he acknowledged that efficacy was not 100%.[60] Subsequently longer acting depot penicillins were recommended,[4,62] which were in turn replaced by single dose benzathine penicillin G. These treatments had not been evaluated in infants; evidence for the efficacy of these regimens had been extrapolated from experience in adults.[63] Nevertheless by 1968 the recommended dose of 50 000 units/kg of benzathine penicillin G was established.[64]

These regimens were challenged in the early 1970s.[65] Earlier studies in adults and animals suggested that a penicillin concentration in serum of 0.018 μg/ml should be maintained over 7 to 10 days to cure primary or secondary syphilis.[66] Procaine penicillin[67,68] but not benzathine penicillin G[69,70] was found to maintain this concentration in both serum and CSF of neonates, and was recommended at 50 000 units/kg daily, as treatment for congenital neurosyphilis. Crystalline penicillin, 50 000 units/kg/day, was also recommended as treatment[71] although this drug is pharmacologically different from procaine penicillin[67] and despite evidence that administration of this dose of crystalline penicillin for 17 days failed to clear *T. pallidum* from the aqueous humor of an infant.[72] (Although this is the only failure reported with this regimen, few infants have been studied as carefully.)

Because of this concern CDC recommends that the dose of crystalline penicillin for neonates with congenital syphilis be increased to 50 000 units/kg/dose intravenously every 8 to 12 hours for 10 to 14 days.[2] Although this dose is somewhat arbitrary, it is comparable to that normally administered to an infant with bacterial meningitis.[73] The efficacy of this therapy for congenital syphilis given coinfection with human immunodeficiency virus is unknown.

The use of benzathine penicillin G has been problematic. Benzathine penicillin G was considered an acceptable alternative[74,75] "if neurosyphilis is ruled out" until reports were published of three infants who developed clinically manifest congenital syphilis after receiving such treatment.[76,77] Subsequently other treatment failures have been reported to CDC. Consequently benzathine penicillin G is no longer recommended as an alternative therapy for infants with congenital syphilis. Both the American Academy of Pediatrics and CDC now recommend treating all infants born to women with untreated syphilis with parenteral penicillin for 10 to 14 days regardless of clinical examination or laboratory findings.[2,73]

Despite this benzathine penicillin G may be acceptable treatment in certain situations. The failures that were reported occurred among two groups of asymptomatic infants: (1) those who were not fully evaluated for evidence of congenital syphilis; and (2) those whose mothers clearly had early syphilis. If such infants are excluded the likelihood of a clinical treatment failure with benzathine penicillin G is negligible, well below the 3% previously mentioned in the literature,[76] in part because many of the asymptomatic infants eligible for this treatment are not infected. Indeed the 3% figure is probably an overestimate. Data for this calculation were obtained from the congenital syphilis reporting system, which significantly undercounted the number of asymptomatic infants treated with benzathine penicillin (the "denominator") but more ac-

curately counted symptomatic infants who presented as treatment failures (the "numerator").

For these reasons and because the number of cases of congenital syphilis is increasing, further burdening health care resources, CDC developed criteria for selecting infants for whom benzathine penicillin G would be appropriate therapy.[2] Use should be limited to infants who, after evaluation, do not have clinical or laboratory signs of congenital syphilis, and whose mothers do not have untreated syphilis. An infant who has no evidence of disease after clinical and laboratory evaluation and whose mother has a low serologic titer, no clinical signs of syphilis and an uncertain history of treatment is probably not infected. Nevertheless if follow-up is not assured (the usual situation), such infants require treatment, which involves extended hospitalization or outpatient therapy for penicillin administration if benzathine penicillin G were not an option. In these circumstances benzathine penicillin G is an attractive therapy, because it reduces both health care costs and the risk of complications that accompany parenteral treatment for 10 days. Similarly benzathine penicillin G may be appropriate treatment for another group, infants whose mothers received antepartum treatment inadequate for the fetus (i.e. erythromycin or treatment late in pregnancy) and who have no evidence of congenital syphilis (including long bone radiographs and CSF analysis).[2]

EVALUATING AN INFANT FOR CONGENITAL SYPHILIS: ASSESSING MATERNAL TREATMENT

CDC has formulated guidelines for the evaluation and management of infants at risk for congenital syphilis. This algorithm (Fig. 2) is based on results of evaluation of the infant and on the likelihood that the mother has active infection. Note that asymptomatic infants do not need evaluation if their mothers were "successfully" treated.

The following definitions should help clarify the recommendations. "Adequate therapy" during pregnancy is penicillin therapy, appropriate for the stage of syphilis in the mother, started at least 30 days before delivery.[2] In prospective studies the efficacy of 2.4 million units of penicillin appeared excellent regardless of gestation.[4, 78, 79] Treatment failures have been reported, however, and are most associated with therapy in the month before delivery.[4, 13, 78-81] Such failures may occur because standard doses of antibiotics result in lower serum concentrations later in pregnancy (maternal plasma volume has increased[82]) or because the efficacy of benzathine penicillin therapy appears to lessen when infection in the fetus has become established (as identified by hydrops or hepatosplenomegaly on ultrasound examination). Although failures of benzathine penicillin are rare when therapy is administered more than 1 month before

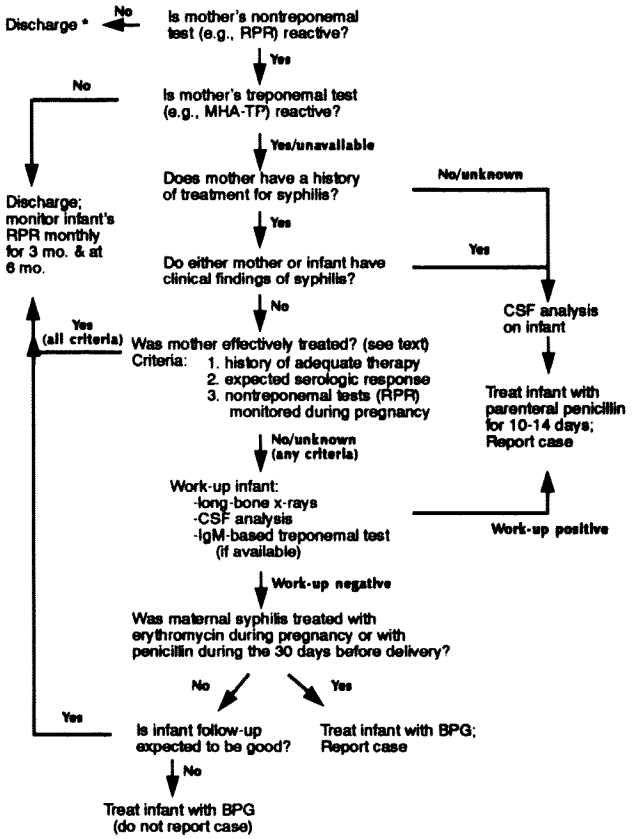

FIG. 2. Algorithm for evalation and management of mothers and infants. *MHA-TP*, microhemagglutination assay for antibodies to *T. pallidum*; *BPG*, benzathine penicillin G; *DFA*, direct fluorescent antibody.

delivery, some experts evaluate any infant whose mother was treated after 20 weeks of gestation, regardless of her serologic response to therapy.[58] Finally non-penicillin regimens are not considered "adequate"; transplacental passage of erythromycin is variable and many failures have been reported.[83]

Determining whether an "expected serologic response" occurred after therapy requires clinical judgment. After successful treatment of primary or secondary syphilis, the titer of nontreponemal antibody tests should drop 4-fold or more within 3 months. Slower responses occur in patients who have had syphilis previously or who have latent disease.[84] If patients have latent syphilis, nontreponemal test titers may not disappear but stabilize and persist at low levels (less than or equal to 1:2); these are referred to as serofast titers and are more likely to occur in women who have late syphilis. Vertical transmission is not known to occur from mothers who were treated for syphilis and maintained a titer which was serofast. Therefore women who have not demonstrated adequate response to treatment or who cannot be classi-

fied as serofast should be assumed to be infected and their infants should be treated with parenteral penicillin for 10 to 14 days.

All seroreactive women should be monitored with nontreponemal tests during pregnancy. Women treated during pregnancy may still be infected at delivery; benzathine penicillin G is not 100% effective, and reinfection is possible. Only by monitoring titers monthly can the effect of therapy be known. Similarly a declining or stable nontreponemal titer should be documented among women treated before they were pregnant if they are still seroreactive while pregnant. In either case when maternal titers, monitored through pregnancy, indicate that treatment was successful (declining or serofast titer), the infant does not need to be evaluated or treated. If there is any doubt about the success of the treatment the infant should be fully evaluated. If there is no evidence of congenital syphilis clinicians may monitor the infant's nontreponemal test titer monthly; the tests should be nonreactive by 3 to 6 months of age. (In contrast, treponemal tests in the infant may be reactive throughout the first year of life because of persistence after passive maternal transmission.[6])

CONCLUSION

Recent CDC guidelines permit design of an algorithm to ensure that all infected infants receive appropriate treatment and to minimize the number unnecessarily treated. However, the lack of a sensitive, specific test to identify active syphilis means that the decision to treat asymptomatic newborns must be based on evaluation of mother and infant and of the likelihood of adequate follow-up; it also means that the diagnosis of congenital syphilis remains complicated, that optimal treatment remains unknown and that guidelines for management and reporting remain controversial.

ACKNOWLEDGMENTS

Larry Taber (Baylor University) and Sandra Larsen (CDC) helped with informative discussions; George Schmid reviewed the manuscript critically; Marie Morgan provided editorial review.

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