

The Role of Pediatric Pharmacists in the Prevention and Treatment of Congenital Syphilis

Taylor Barnes, PharmD and Jennifer E. Giroto, PharmD on behalf of the Advocacy Committee of the Pediatric Pharmacy Association

In recent years, rates of syphilis in adults have been on the rise resulting in an increase in the number of neonates born with congenital syphilis. National organizations including the Centers for Disease Control and Prevention as well as The US Preventative Services Task Force recommend routine testing of pregnant persons to identify and provide maternal syphilis treatment prior to delivery. Significant variability exists between states for these screenings, resulting in some pregnant persons not being diagnosed prior to delivery. The Pediatric Pharmacy Association (PPA) believes that pharmacists, along with other health care providers can help by ensuring optimal syphilis testing and treatment pathways for pregnant individuals and newborns are included in their workplaces. PPA also supports pharmacists working to increase treatment compliance by providing medication education and counseling regarding optimal treatment of syphilis infections, as well as work with state and local governments to standardize treatment recommendations.

KEYWORDS congenital infection; congenital syphilis; neonatal illnesses; public health; *Treponema pallidum*

J Pediatr Pharmacol Ther 2024;29(4):429–433

DOI: 10.5863/1551-6776-29.4.429

Background

Syphilis is a sexually transmitted infection (STI) that is caused by the bacteria *Treponema pallidum*. The rates of syphilis have been increasing at a dramatic rate in the United States. The number of syphilis cases diagnosed increased by approximately 70,000 from 101,590 in 2017 to 171,074 in 2021. This increase results in an estimated prevalence of 74 cases of syphilis per 100,000 population in 2021.¹ Unfortunately, when a pregnant individual is infected with syphilis, it can also be passed to the developing fetus/newborn infant. This passing of syphilis to the fetus/infant is called congenital syphilis. Congenital syphilis can result in premature death (e.g., miscarriage, stillbirth, or early infant death) or long-term effects on the brain or bones of the infant.² The rates of congenital syphilis have also been increasing dramatically from 335 cases in 2012 to 3761 cases in 2022.³

Congenital syphilis is a reportable condition in all 50 states. The current definition for congenital syphilis includes live and stillborn infants who have positive reactive tests for syphilis born to mothers who received either no or partial treatment. Congenital syphilis has mostly affected non-Hispanic Blacks (39%) and Hispanics (32%) followed by non-Hispanic Whites (21%).^{1,2} Less than 5% of congenital syphilis cases were reported in American Indian/Alaskan Natives or Asian/Pacific Islanders.^{1,2} Regional variations were also reported with most cases of congenital syphilis occurring in the South and West regions of the United States (52% and 36%, respectively), while

the Midwest and Northeast each report less than 10% of cases.^{1,2}

The consequences of congenital syphilis are significant. A meta-analysis published in 2013 reported syphilis infection during pregnancy (versus those without syphilis) resulted in a 21% increased rate of fetal loss or stillbirth, 9% neonatal death, and among those who lived, a 6% increased risk of prematurity or low birthweight, and 15% clinical symptoms of syphilis at birth.⁴ More recent reports of those born with congenital syphilis from 2014–2018 noted 38.1% had some clinical symptoms of congenital syphilis at birth (e.g., rash, snuffles [or loud sniffing upon breathing], hepatosplenomegaly), and 6.4% were stillborn.⁵ Cost to the health care system for infants needing to undergo treatment for congenital syphilis after birth are estimated to include admission for 7.5 days following birth with an associated health care cost of \$5,700 to \$16,700.⁶ Congenital syphilis can be prevented by appropriate screening of pregnant persons and treating those found to be infected with syphilis with intramuscular penicillin at least 30 days prior to delivery. Missed opportunities for identifying or treating pregnant individuals infected with syphilis have been categorized as follows: insufficient treatment of the pregnant individual's identified syphilis infection, lack of prenatal care resulting in no testing for syphilis, or lack of syphilis testing while receiving routine prenatal care. Of those born with congenital syphilis in 2022, 37% of pregnant persons had non-timely or no documented test for syphilis in

pregnancy, 5.2% had late identification of seroconversion, and 58% had timely testing. Of the 58% with timely testing, 19% had no treatment and 69% had inadequate treatment.³ In this report, the Northeast, Midwest, and West demonstrated high rates of lack of testing while the South was noted to have inadequate treatment as the highest barrier to prevention of congenital syphilis. When Race and Ethnicity of the pregnant person were investigated almost all groups investigated had high rates of lack of testing and inadequate treatment (e.g., >25%). Differences in the most common reason were noted—American Indian/Alaskan Natives, Asians, Native Hawaiian/Pacific Islanders, Whites, and multiracial groups were noted to have lack of testing as the highest missed opportunity reported, while inadequate treatment was the most frequent missed opportunity in Blacks/African Americans, Hispanics/Latinos, or other race/ethnicities.³

The Centers for Disease Control and Prevention (CDC) STI treatment guidelines and the US Preventative Services Task Force (USPSTF) have both recommended that all pregnant individuals be screened for syphilis at their first prenatal visit (or at delivery if no prenatal care has occurred).^{7,8} The CDC recommends additional testing around 28 weeks' gestation and at delivery for those who either are in a region with high rates of syphilis or if the patient is at high risk for acquiring syphilis during pregnancy.⁷ Lastly, the CDC recommends that anyone who delivers a stillbirth at 20 weeks or later gestation should also be tested.⁷ Not all states, however, mandate syphilis testing in pregnancy that is in line with the USPSTF and legislation surrounding testing is sporadic and inconsistent across the United States.

In a review of state statutes and regulations regarding prenatal syphilis screening that was published by the CDC in 2020, most states do mandate testing at the first prenatal visit, which is in line with CDC recommendations (Table 1).^{9,10} All but 8 states require syphilis testing at least at the first pregnancy visit. However, many states do not include any recommendations for further testing for pregnant individuals, even those who are at high risk of contracting syphilis during pregnancy. This accounts for 62% of states in the United States that have more relaxed recommendations for prenatal syphilis testing. Notably, some states recommend prenatal screening for syphilis more frequently than what is recommended by the CDC, either mandating testing 2 or 3 times during pregnancy. As shown in Table 1, generally the states with higher incidence of congenital syphilis oftentimes, but not always, are the states with increased frequency of recommended testing.^{9,10} In those areas with less rigorous testing, the diagnosis of congenital syphilis may be delayed to later in the pregnancy.^{9,10}

The CDC recommends using a 2-step testing algorithm to detect syphilis.⁷ The first step is the non-treponemal antibody test which can be either the

Table 1. Summary of State Congenital Syphilis Laws and Incidence of Congenital Syphilis^{9,10}

Category	States*	Reported Congenital Syphilis Incidence Range Per 100,000 Population 2020
Do not require syphilis testing at even the first pregnancy visit	HI, IA, ME, MN, MS, NH, ND, WI	0–101 (median of the states 10.5)
Only recommended syphilis testing at first pregnancy visit	AK, CA, CO, ID, KS, KY, MA, MT, NE, NM, NY, OH, OK, OR, RI, SC, SD, UT, VT, VA, WA, WV, WY	0–182.9 (median of the states 23.55)
Syphilis testing at first pregnancy visit and additional testing if at high risk	MO, TN, PA, IN	7.4–41.6 (median of the states 24.45)
Syphilis testing 2–3 times during pregnancy/delivery	AL, AZ, AR, CT, DE, DC, FL, GA, IL, LA, MD, MI, NJ, NV, NC, TX	5.8–151.2 (median of the states 35.8)

* Standard, generally accepted abbreviations for States are listed in the table.

venereal disease research laboratory (VDRL) or rapid plasma reagin (RPR) test. If this non-treponemal antibody test is positive, confirmation is determined using a treponemal antibody test. Note, newer automated testing may provide a treponemal test that per CDC guidelines should be reflexed to a non-treponemal test. If there is discordance, the guidelines should be referred to for specific next steps.⁷

Once it is determined that a patient is positive, the treponemal test does not need to be repeated. Instead, the non-treponemal test will be used to evaluate treatment response.^{7,8} Pregnant individuals that are confirmed to be positive should be treated with intramuscular benzathine penicillin. Current CDC guidelines are summarized in Table 2.⁷ These guidelines suggest those patients diagnosed with primary, secondary, or early latent syphilis receive 1 or 2 doses of 2.4 million units of penicillin; if 2 doses are administered, they should be separated by 7 days. For more progressed forms of syphilis treatment, refer to CDC recommendations.⁷ The treatment is most successful in those who complete therapy at least 30 days prior to delivery.²

To evaluate efficacy of therapy, pregnant patients should be followed post treatment with a non-treponemal test with at least a 4-fold decrease in titers to demonstrate adequate response to therapy. The timing of the follow-up testing depends upon treatment timing. If the pregnant individual receives penicillin treatment before 24 weeks' gestation, retesting can be obtained 8 weeks later. All patients (i.e., those with and without repeat testing results) should also have a non-treponemal follow-up test at delivery and at any time if there is concern for reinfection or failure.⁷

After delivery, it is recommended that neonates born to individuals with a positive syphilis screen should have an RPR or VDRL performed and be physically examined for signs of congenital syphilis.⁷ Importantly, neonatal testing is not useful without maternal titers as differentiation of maternal and newborn antibodies is unreliable. Treatment of neonates and infants born to mothers with syphilis differs based on clinical exam findings, infant and maternal laboratory findings, and maternal compliance to treatment. Recommendations for treatment of congenital syphilis can be found in Table 3.⁷

Rationale and Recommendations

Due to the significant negative consequences of congenital syphilis and the simple treatment regimen required, advocacy efforts are necessary to ensure pregnant patients are screened and treated in line with the CDC recommendations (Table 2).⁷ The Pediatric

Pharmacy Association (PPA) believes that clinical pharmacists working with hospital-based clinicians and obstetrics and gynecology specialists can work to increase testing of pregnant individuals for syphilis. This is important, especially to identify high-risk populations, even in states where the regulatory statutes mandate less aggressive testing strategies than recommended by the CDC. A syphilis testing and treatment protocol for pregnant individuals and newborns can be beneficial in optimizing testing and treatment outcomes, both of which have been shown to be barriers to identification of syphilis in pregnant individuals. In addition, PPA endorses the important role inpatient and ambulatory pharmacists have as an integral part of the successful implementation of an evidence-based pathway, providing expertise to both the development of such pathway and adherence to the pathway in daily multidisciplinary rounds, patient chart review, and ambulatory clinic follow up. Even in the absence of a standardized institutional protocol, pharmacists should be involved in ensuring optimal treatment of syphilis as part of rounding and patient care activities. This is particularly important due to the variety of penicillin products available and the differences in dosing regimens dependent on the product selected. Pharmacists can also serve as a resource regarding use of alternative therapies, such as doxycycline, in lactating individuals. While there is some concern

Table 2. CDC Recommended Syphilis Treatment for Pregnant Persons⁷

Stage of Syphilis	Treatment
Primary, secondary, or early latent	Benzathine penicillin G 2.4 million units IM × 1; CDC notes that a second dose may be considered 1 wk later (Note: the second dose is only for pregnant individuals to help prevent congenital syphilis)*
Late latent, latency of unknown duration, or tertiary syphilis with normal cerebral spinal fluid	Benzathine penicillin G 2.4 million units IM weekly for 3 wk*
Neurosyphilis or ocular syphilis	Aqueous crystalline penicillin G 3–4 million units per dose every 4 hr or 18–24 million units per day as continuous infusion for 10–14 days

CDC, Centers for Disease Control and Prevention; IM, intramuscular
* Currently on national shortage.

Table 3. CDC Treatment Recommendations for Congenital Syphilis^{7,13}

Likelihood of Congenital Syphilis	Recommended Treatment
Confirmed proven or highly probable congenital syphilis	Aqueous crystalline penicillin G 50,000 units/kg/dose every 12 hr through 7 days old then 50 units/kg/dose every 8 hr for a total of 10 days
Possible congenital syphilis	Aqueous crystalline penicillin G 50,000 units/kg/dose every 12 hr until 7 days old and then 50,000 units/kg/dose every 8 hr for a total of 10 days OR Benzathine penicillin G 50,000 units/kg/dose IM once*
Congenital syphilis less likely	Benzathine penicillin G 50,000 units/kg/dose IM once* Or some cases may have no initial treatment, but instead very close follow-up and monitoring
Congenital syphilis unlikely	None

CDC, Centers for Disease Control and Prevention; IM, intramuscular
* Currently on national shortage.

that doxycycline exposure in breastfeeding individuals would cause adverse effects in infants (e.g., teeth staining), LactMed in line with the American Academy of Pediatrics' Redbook suggests short courses, which they define as less than 21 days, of doxycycline exposure to any age pediatric patient, is generally considered safe.^{11,12} In addition, during medication shortages, PPA continues to support active pharmacist involvement in education and prioritization efforts to ensure that the Bicillin L-A (benzathine penicillin G) is prioritized to be administered to pregnant persons and infants when indicated, as the CDC only recommends penicillin based regimens (versus alternative like ceftriaxone or doxycycline) for these populations.¹³ Pharmacists are perfectly poised to be involved in patient counseling and education regarding penicillin, ceftriaxone, or doxycycline regimens and potential adverse effects to ensure optimal patient follow up.

Education of all hospital personnel as well as public health workers, regarding the consequences of untreated syphilis, both for individuals and infants, is also necessary to further increase advocacy efforts across the United States. Pharmacists can be vital to these advocacy efforts, providing education to providers about the importance of treatments and lack of complications associated with the intramuscular penicillin utilized for treatment of the pregnant individual. In addition, increased awareness of syphilis among the public, including individuals of childbearing age, is crucial to optimize the involvement of people in their care and for patients to be involved in advocacy efforts within their state. Increased awareness regarding the rates of congenital syphilis in the community and risk factors for a pregnant individual for syphilis infections are needed. The importance of this patient education is heightened due to the lack of standard testing recommendations between states. Pharmacists can be involved in these advocacy efforts through participation in public health fairs, volunteering and educational initiatives at free medical clinics, and involvement with local health departments to develop educational materials.

Additionally, increased advocacy efforts across state governments to create a standardized approach to testing is recommended. Advocacy efforts at the state and local level in the United States, as well as international efforts are necessary. Increasing syphilis rates is not a problem exclusive to the United States, and as people continue to travel and migrate more frequently, there is increased need for transparency and testing worldwide. As in the United States, recommendations for prenatal syphilis testing differ widely between countries. All those mentioned previously, including physicians, nurse practitioners, physician assistants, nurses, pharmacists, and public health officials, can contribute to international and national advocacy ef-

forts related to improving care and reducing rates of congenital syphilis.

Lastly, due to the variety of testing that is employed in the prenatal period, health care providers may be uninformed about the risk of congenital syphilis when taking over the care of a newborn. Ensuring availability to results and awareness of testing and treatment of pregnant individuals as part of the delivery to nursery or neonatal intensive care unit sign off can be vital for getting infants receiving appropriate testing and treatment to prevent consequences of congenital syphilis. Pharmacists can be involved in following up maternal testing and treatment as part of daily multidisciplinary rounds or daily chart review. Increased transparency regarding testing may also decrease health care costs and reduce unnecessary testing or complications from missed cases.

Conclusion

Cases of congenital syphilis have increased year over year since 2013 and can have devastating impacts to babies, including early infant death, blindness, deafness, and other developmental problems. There are a variety of reasons cited why congenital syphilis continues to be passed from pregnant individuals to infants, including insufficient treatment of the pregnant individuals identified syphilis infection, lack of prenatal care resulting in no testing for syphilis, or lack of syphilis testing while receiving routine prenatal care. However, if detected during pregnancy, complications and infection of the newborn can be prevented. Pediatric pharmacists should be involved in efforts to improve the detection and treatment of syphilis and congenital syphilis by advocating for optimal syphilis testing and treatment, providing medication education and counseling to pregnant individuals diagnosed with syphilis and by working toward the advancement of standardized testing and treatment recommendations with their state and local governments.

Article Information

Affiliations. Department of Pharmacy (TB), Orlando Health, Orlando, FL; Department of Pharmacy Practice (JG), University of Connecticut, Storrs, CT; Division of Infectious Diseases and Immunology (JG), Connecticut Children's, Hartford CT.

Correspondence. Taylor Barnes, PharmD, BCPPS; taylor.barnes@orlandohealth.com

Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Submitted. March 22, 2024

Accepted. March 22, 2024

Copyright. Pediatric Pharmacy Association. All rights reserved.
For permissions, email: membership@pediatricpharmacy.org

References

1. Centers for Disease Control and Prevention. Preliminary 2021 STD surveillance data. National overview. Accessed March 3, 2023. <https://www.cdc.gov/std/statistics/2021/default.htm>
2. Kimball A, Torrone E, Miele K, et al. Missed opportunities for prevention of congenital syphilis - United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2020;69(22):661–665.
3. McDonald R, O'Callaghan K, Torrone E, et al. Vital signs: missed opportunities for preventing congenital syphilis - United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72(46):1269–1274.
4. Gomez GB, Kamb ML, Newman LM, et al. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. *Bull World Health Organ*. 2013;91(3):217–226.
5. Kimball A, Bowen VB, Miele K, et al. Congenital syphilis diagnosed beyond the neonatal period in the United States: 2014–2018. *Pediatrics*. 2021;148(3):e2020049080.
6. Owusu-Eusei KJ, Introcaso CE, Chesson HW. Hospitalization cost of congenital syphilis diagnosis from insurance claims data in the United States. *Sex Transm Dis*. 2013;40(3):226–229.
7. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1–187.
8. Curry SJ, Krist AH, Owens DK, et al; US Preventive Services Task Force. Screening for syphilis infection in pregnant women: US Preventive Services Task Force reaffirmation recommendation statement. *JAMA*. 2018;320(9):911–917.
9. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2020. Centers for Disease Control and Prevention sexually transmitted disease surveillance web site. Accessed March 31, 2023. Updated 2020. <https://www.cdc.gov/std/statistics/2020/tables/20.htm>
10. Centers for Disease Control and Prevention. Sexually transmitted diseases (STDs), state statutory and regulatory language regarding prenatal syphilis screenings in the United States. Accessed March 9, 2023. <https://www.cdc.gov/std/treatment/syphilis-screenings.htm>
11. National Institutes of Health. Doxycycline. LactMed. Drugs and lactation database. 2021. Accessed February 9, 2024. <https://www.ncbi.nlm.nih.gov/books/NBK500561/>
12. Kimberlin D, Barnett E, Lynfield R, et al. Syphilis. In: Redbook: 2021–2024 Report of the Committee on Infectious Diseases. American Academy of Pediatrics. 2021: 729–744.
13. Bachmann L, Mena L; Centers for Disease Control and Prevention. Clinical reminders during Bicillin L-A shortage. Updated 2023. <https://www.cdc.gov/std/dstdp/dcl/2023-july-20-Mena-BicillinLA.htm> Accessed 20 March 2023.