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Evaluations and Treatment among Infants Exposed to Syphilis in Utero, Six U.S. States, 2018–2021

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Abstract

Contemporary data on evaluations and treatment of infants exposed to syphilis in utero are limited. This study analyzed population-based surveillance data to describe the management of exposed infants. Findings indicate inconsistent implementation of recommended guidelines for evaluations and treatment of infants exposed to syphilis in utero.

SUMMARY

Surveillance data from six U.S. states show inconsistent evaluations and treatment for infants exposed to syphilis in utero. Collaboration with public health can improve recognition of syphilis exposure, increase coordination of recommended care, and improve infant outcomes.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Keywords

congenital syphilis; congenital infection; STI Treatment Guidelines; public health; surveillance

Introduction

The incidence of congenital syphilis (CS) continues to rise in the United States with >740% increase from 2014 to 2023[1], despite available preventative measures.[2,3,4] Evaluations and treatment for syphilis in pregnancy and CS are complex.[5] The Centers for Disease Control (CDC) Sexually Transmitted Infections (STI) Treatment Guidelines and the American Academy of Pediatrics guidelines recommend evaluations and treatment for infants born to women with syphilis during pregnancy based on clinical scenarios of likelihood of CS, dependent on maternal treatment and infant laboratory and physical exam findings.[3,4,6] Provider surveys have found varied approaches in care of exposed infants, but real-world data are outdated or geographically limited.[7,8] Some infants who are clinically recommended to receive treatment (those classified as CS less likely) are not identified by the Council of State and Territorial Epidemiologists (CSTE) surveillance case definitions and not included in national surveillance data.[4,9]

Using a population-based surveillance cohort, we describe evaluations and treatment patterns by clinical scenario among infants exposed to syphilis in utero.

Methods

The Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET) collects enhanced syphilis surveillance data in select U.S. jurisdictions.[10,11] Six states (Arizona, Georgia, Michigan, New Jersey, New York [excluding New York City], and Washington) ascertained syphilis during pregnancy through national notifiable disease reporting and linkages with vital records.[11] Data were collected using case reports, medical records, vital records, and laboratory results. Infants born January 1, 2018–December 31, 2021 were included if the woman met the CSTE case definition for syphilis during pregnancy or infant met probable or confirmed CS CSTE case definitions.[9] Analysis included infants with completed birth hospitalization medical record abstraction and were reported to SET-NET as of June 7, 2024.

Infants were categorized into clinical scenarios per STI Treatment Guidelines: 1) *confirmed or highly probable CS* defined as having a positive darkfield test OR abnormal physical examination with signs consistent of CS OR an infant nontreponemal serologic titer ≥fourfold the maternal titer at delivery; 2) *possible CS* defined as not meeting scenario 1 AND inadequate or no maternal syphilis treatment in pregnancy; or 3) *CS less likely* defined as not meeting scenario 1 AND adequate maternal treatment in pregnancy.[3,4] Adequacy of maternal treatment was based on receipt of recommended type, timing (>30 days before delivery), and dosing per STI Treatment Guidelines.

STI Treatment Guidelines recommend all infants with confirmed or highly probable CS receive 10 days of penicillin treatment, cerebrospinal fluid (CSF) evaluations, and complete

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blood count with differential (CBC/D). Long-bone radiographs were recommended "as clinically indicated" in 2015 guidelines and for all in 2021.[3,4] For the remaining scenarios, guidelines were in alignment across years. Infants with possible CS are recommended to either have 10 days of treatment, or a single dose of penicillin provided they have a normal CSF evaluation, long-bone radiographs, and CBC/D. Infants with CS less likely are recommended to receive one dose of penicillin or have close serologic follow-up. All infants with reactive nontreponemal titers at birth are recommended to have follow-up serologic testing.

Descriptive analyses were presented by CS clinical scenarios and by gestational age, neonatal intensive care unit (NICU) admission and nontreponemal testing. Clinical scenario-based recommended evaluations included CSF analyses and long-bone radiographs. Treatment categories reported included 10 days of aqueous crystalline penicillin G (PenG) or procaine PenG (10 days of PenG), one dose of benzathine penicillin G (BPG), other treatment (other non-recommended penicillin or non-penicillin-based treatment), or no reported treatment (to the health department or in the birth hospital medical record). In a sub-analysis of infants with reactive nontreponemal titers at birth and follow-up data available up to 9 months, we reported frequency of follow-up serologic testing.

Analyses were conducted using R version 4.4 (R Foundation) statistical software. This activity was reviewed by CDC and conducted consistent with applicable federal law and policy (*45 C.F.R. part 46.102(l)(2), 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a*).

Results

A total of 1636 infants met inclusion criteria; 6 received an incomplete course of treatment with 4 to 7 days of aqueous PenG (5 with possible CS and one CS less likely) and were considered unclassifiable and excluded from the analysis. Of the remaining 1630 (resulting from 1604 pregnancies, Supplementary Table), 179 (11.0%) infants were categorized as confirmed or highly probable CS, 588 (36.1%) as possible CS, and 863 (52.9%) as CS less likely (Table 1).

Of 179 infants with confirmed or highly probable CS, 81 (45.3%) were preterm, and 138 (77.1%) were admitted to a NICU. Two-thirds (67.0%) were reported to have received the recommended 10 days of PenG. Twenty-six (14.5%) received one dose of BPG, and 33 (18.4%) had other or no treatment. Long-bone radiographs were reported for 47.5% and CSF for 49.2%.

Of 588 infants with possible CS, 143 (24.3%) were preterm, and 330 (56.1%) were admitted to a NICU. The majority, 364 (61.9%) received 10 days of PenG, while 74 (12.6%) received one dose of BPG. Of those receiving one dose, only 9 (12.2%) had normal CSF reported by date of treatment. Other or no treatment was reported for 150 infants (25.5%).

Of 863 infants categorized as CS less likely, 124 (14.4%) received 10 days of PenG, and 270 (31.3%) received one dose of BPG. Half (54.3%) had other or no treatment reported. While not universally recommended for this scenario, 11.4% had long-bone radiographs reported

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and 11.1% CSF. Of those receiving 10 days of PenG, 29.0% (36/124) had elevated CSF or abnormal long bone radiograph findings reported.

For 881 infants with a reactive nontreponemal test at birth, 606 (68.8%) had well-child visit data (>28 days to <9 months of age) or laboratory data submitted after birth hospitalization. Nontreponemal testing at follow-up was reported for 38.2% of infants with confirmed or highly probable CS, 33.6% with possible CS, and 24.4% with CS less likely. Among 295 infants with CS less likely who had follow-up data, 81 (27.5%) were not treated at birth, and of those, only 22 (27.2%) had close serologic follow-up as recommended.

Discussion

We observed inconsistencies of recommended evaluations and treatment across all clinical scenarios during birth hospitalization and early infancy identified by health departments. While most infants with confirmed or highly probable CS received some type of treatment, only two-thirds were identified by the health department as having had the full 10-day recommended course of treatment. Only half of infants in this scenario had CSF evaluations reported. For this scenario the results do not impact treatment decisions, and there is debate about the necessity for invasive lumbar punctures.[12]

For infants with possible CS, CSF and long-bone radiographs impact length of treatment and follow-up. Among infants who received one dose, many did not have the recommended evaluations reported for this treatment option. A quarter of infants with possible CS had other or no treatment reported.

Of infants with CS less likely, 14.4% received longer length of treatment than recommended (10 days of intravenous or intramuscular therapy). Nearly a third of these infants with longer length treatment had abnormal CSF or radiograph findings, despite being not universally recommended for this group. Importantly, surveillance data lack nuanced details of clinical decision-making that may lead to longer treatment durations.

Per STI Treatment Guidelines, infants with a reactive nontreponemal test should receive follow-up every two to three months until nonreactive.[4] Across all clinical scenarios, few infants (29.7%) with reactive nontreponemal tests received follow-up nontreponemal tests. Infants may not receive follow-up testing because of limited access to care, lack of communication, or missed opportunities at attended well child or vaccination visits.[2,7]

Given the recent surge of CS, providers may also be unfamiliar with guidelines. One survey conducted in 2024 showed that of 442 pediatric providers, 94.1% selected to evaluate and manage infants with confirmed or highly probable CS as recommended, yet only 45.8% did the same for infants with CS less likely.[7] Identifying and strengthening partnerships between birthing facilities and local public health can improve communication and care.

This large, population-based analysis utilized surveillance data from six jurisdictions representative of areas with high CS prevalence. However, there are several limitations. First, nontreponemal titers were unavailable for 25.1% (364/1451) of infants classified as possible CS and CS less likely and we depended on maternal treatment to classify these

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cases, which may result in possible misclassification of infant scenario. Second, surveillance data are subject to missing data (e.g., transfers to tertiary care, loss to follow-up, or poor documentation) which could lead to differential underreporting of both evaluations and treatment received. Third, these surveillance data do not capture CBC/D values, which could influence individual treatment decisions.[3,4] Finally, many complex and unmeasured factors go into clinical decision making (e.g., lack of communication regarding maternal data or nonspecific physical exam findings). Some nonspecific findings may lead an infant to meet criteria for confirmed or highly probable CS; however, clinicians may determine these are attributable to other conditions and not CS. As such, strict application of confirmed or highly probable criteria may lead to overestimation of cases in that category.

Public health plays a critical role in the primary and secondary prevention of CS, ensuring maternal information is available to providers caring for infants and providing resources and guidance regarding recommended treatment and follow-up care. Despite available guidelines, diagnoses of CS are missed and, even among infants known to be exposed, information needed to make treatment decisions may be unavailable.[2,5,13] These findings emphasize the need for accessible education or consultation (e.g., through the National Network of STD Clinical Prevention Training Centers), system-level supports (e.g., integrated clinical pathways), and continued collaboration and coordination between public health and clinical partners to ensure all infants exposed to syphilis in utero receive recommended care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BPG	Benzathine Penicillin G
CBC/D	Complete Blood Count with Differential
CS	Congenital Syphilis

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CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
NICU	Neonatal Intensive Care Unit
PenG	Penicillin G
SET-NET	Surveillance for Emerging Threats to Mothers and Babies Network
STI	Sexually Transmitted Infections
VDRL	Venereal Disease Research Laboratory

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Table 1.

Characteristics, evaluations, and treatment among infants exposed to syphilis in utero, 6 U.S. States, 2018–2021

	Total (N=1630)	Confirmed or Highly Probable Congenital Syphilis (CS)[a] (N=179)	Possible CS[b] (N=588)	CS Less Likely[c] (N=863)
Infant characteristics				
Gestational age				
Term (≥37 weeks)	1307 (80.2%)	98 (54.7%)	445 (75.7%)	764 (88.5%)
Preterm (< 37 weeks)	323 (19.8%)	81 (45.3%)	143 (24.3%)	99 (11.5%)
Neonatal intensive care unit admission				
Overall	681 (41.8%)	138 (77.1%)	330 (56.1%)	213 (24.7%)
Among infants ≥35 weeks	523 (32.1%)	77 (43.0%)	269 (45.7%)	177 (20.5%)
Infant nontreponemal testing at birth				
Yes	1240 (76.1%)	153 (85.5%)	470 (79.9%)	617 (71.5%)
Reactive	881 (54.0%)	127 (70.9%)	345 (58.7%)	409 (47.4%)
Non-reactive	359 (22.0%)	26 (14.5%)	125 (21.3%)	208 (24.1%)
Not reported	390 (23.9%)	26 (14.5%)	118 (20.1%)	246 (28.5%)
Infant evaluation at birth				
Cerebrospinal fluid (CSF) analysis performed	446 (27.4%)	88 (49.2%)	262 (44.6%)	96 (11.1%)
Any CSF abnormalities[d]	224 (13.7%)	49 (27.4%)	128 (21.8%)	43 (5.0%)
Long-bone radiographs	460 (28.2%)	85 (47.5%)	277 (47.1%)	98 (11.4%)
Abnormalities consistent with CS	64 (3.9%)	24 (13.4%)	33 (5.6%)	7 (0.8%)
Both CSF and long-bone radiographs	298 (18.3%)	62 (34.6%)	174 (29.6%)	62 (7.2%)
Any abnormalities	176 (10.8%)	40 (22.3%)	100 (17.0%)	32 (3.7%)
Infant treatment at birth				
10 days of aqueous crystalline penicillin G or procaine penicillin	608 (37.3%)	**120 (67.0%)**	**364 (61.9%)**	124 (14.4%)
1 dose of benzathine penicillin G	370 (22.7%)	26 (14.5%)	**74 (12.6%)**	**270 (31.3%)**
Other treatment[e]	42 (2.6%)	7 (3.9%)	15 (2.6%)	20 (2.3%)

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No treatment	610 (37.4%)	26 (14.5%)		135 (23.0%)			**449 (52.0%)**	
Reactive nontreponemal titer at birth AND follow-up data available up to 9 months of age	**Total (N=606)**	**Confirmed or Highly Probable CS (N=76)**		**Possible CS (N=235)**			**CS Less Likely (N=295)**	
		Received 10 days (N=58)	**Received 1 dose, other, or none (N=18)**	**Received 10 days (N=178)**	**Received 1 dose (N=27)**	**Received other or none (N=30)**	**Received 10 days or 1 dose (N=205)**	**Received other or none (N=90)**
Any nontreponemal testing between 1–9 months of age	180 (29.7%)	27 (46.6%)	2 (11.1%)	63 (35.4%)	6 (22.2%)	10 (33.3%)	46 (22.4%)	26 (28.9%)

[a] Clinical Scenario 1: Confirmed or highly probable CS defined as an infant having a positive darkfield test OR abnormal physical examination with signs consistent of CS OR an infant nontreponemal serologic titer ≥ fourfold the maternal titer at delivery.

[b] Clinical Scenario 2: Possible CS defined as not meeting clinical scenario 1 AND inadequate or no maternal syphilis treatment in pregnancy.

[c] Clinical Scenario 3: CS less likely defined as not meeting clinical scenario 1 AND adequate maternal syphilis treatment in pregnancy.

[d] Abnormalities include positive Venereal Disease Research Laboratory (VDRL) test, elevated white blood cell count (≥20 cells/mm^3), or elevated protein (≥119 mg/dL).

[e] Other non-recommended penicillin or non-penicillin-based treatment.

Bolded totals indicate acceptable treatment per CDC STI treatment guidelines; however, for some clinical scenarios such as CS less likely acceptable treatment is more complex to distinguish.

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