



# Prevention of congenital syphilis using ceftriaxone in a woman with Stevens–Johnson syndrome reaction to penicillin: A case report

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## ABSTRACT

**Introduction:** The purpose of this report is to increase awareness of ceftriaxone as an alternative therapy for the prevention of congenital syphilis (CS) when the mother is allergic to penicillin, especially when desensitization to penicillin cannot be performed or is unsafe.

**Case:** A 37-year-old pregnant woman who was syphilis positive reacted to penicillin with Stevens–Johnson syndrome (SJS); her rapid plasma reagin (RPR) was 1:64 at presentation to the infectious disease clinic. CS was prevented with two courses of ceftriaxone: 10 days 1 g IV daily at week 12 followed by 10 days of 250 mg IM daily at week 28 achieved a 4-fold fall in RPR titer to 1:16, indicating cure. Full work-up of the neonate according to the guidelines of the American Academy of Pediatrics (AAP) when penicillin is not used in the mother was conducted at birth. In addition to physical exam, syphilis antibodies in blood had an undetectable RPR, a lumbar puncture produced normal cerebrospinal fluid (CSF), and roentgenography of long bones was normal. The child was administered 50,000 units/kg of benzathine penicillin intramuscularly. There were no concerns for allergy or sequela in the mother or neonate at 2-month follow-up with the pediatrician.

**Conclusion:** The goal of this report is to increase awareness of ceftriaxone as an alternative to penicillin in the prevention of CS and to raise the possibility of adjusting AAP guidelines accordingly. However, studies to determine the best route and timing of therapy are necessary.

## 1. Introduction

Untreated or improperly treated syphilis in pregnancy has an 80% chance of fetal infection (1) and is associated with miscarriage, stillbirth, or neonatal death after delivery in 30% of cases (2). Early signs of congenital syphilis (CS) are those that can present at up to 2 years of age and include inflammation of long bones with or without fractures, rash, hepatosplenomegaly, copious nasal discharge (“snuffles”), and central nervous system abnormalities. Symptoms that present after 2 years of age are considered late manifestations and include intellectual disability, physical deformities, and Hutchinson's triad (teeth deformity, interstitial keratitis, eighth-nerve deafness). CS is best prevented by diagnosis and effective treatment of the mother during pregnancy (3); late manifestations are best prevented by treatment within the first three months of life.

There was an 81% rise in syphilis cases between 2014 and 2018; in 2018 alone, there were 1306 CS cases in the United States: an increase of

183% from 462 cases in 2014 (3). Maternal penicillin-based therapy is considered to be the only acceptable method of CS prevention. However, there is little guidance in the literature for what to do if penicillin G benzathine is not available or desensitization therapy cannot be performed, for example in the setting of a severe delayed-type allergy (i.e., Stevens–Johnson syndrome, SJS).

In 2019, the US Centers for Disease Control and Prevention (CDC) reviewed the literature on penicillin alternatives in pregnant women with syphilis where performing desensitization protocols is not feasible or when the supply of benzathine penicillin G is unreliable (4). None of these cases included SJS as a reason for alternative therapy. That review included 6 international publications between 1970 and 2018 and excluded cases where penicillin monotherapy was used. Two studies used ceftriaxone: 11/13 patients received two courses of intramuscular (IM) ceftriaxone therapy and 2/13 patients received amoxicillin/probenecid followed by IM ceftriaxone (ceftriaxone dose range 250–2000 mg), all with prevention of CS (5–8). Tetracycline and macrolide-based

**Abbreviations:** SJS, Stevens–Johnson syndrome; CS, congenital syphilis; CDC, Centers for Disease Control and Prevention; AAP, American Academy of Pediatrics; IM, intramuscular; RPR, rapid plasma reagin; WBC, white blood cell; CSF, cerebrospinal fluid; SCAR, severe cutaneous adverse reactions.

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therapies failed to prevent CS in all eight patients reported (9,10).

## 2. Case Presentation

This is a novel case of syphilis in pregnancy where penicillin desensitization was not possible due to SJS. The patient was a 37-year-old woman who was referred to the infectious diseases clinic as an outpatient by the obstetrics service for treatment of syphilis in pregnancy with a listed penicillin allergy. She tested positive for syphilis with an RPR titer of 1:64 on week 8 of her pregnancy at the first prenatal visit of her third pregnancy. She had no known history of syphilis and was not sure when she acquired it. Based on her being asymptomatic, potential exposure timeline, and significant titer, the patient's condition was classified as early latent syphilis. Regarding her penicillin allergy, four years earlier she had received a week-long course of amoxicillin for strep throat, and the day after she had completed the entire course, she reported lip swelling and tingling followed by desquamation of lips and both hands, which fully resolved without intervention. She could not recall taking penicillin when she was younger. She had not retaken penicillin in the last four years; however, she did report having a prescription for cephalexin but she took only one dose and did not experience any adverse reaction.

Based on this information, she was referred to an allergist, who agreed that no penicillin should be used for her, including during desensitization. Because of the limited alternatives for CS prevention noted in the literature, and after extended discussions with the patient, she was treated at 12 weeks of gestation with a 10-day course of parenteral ceftriaxone 1 g every 24 h in the inpatient setting. She received another 10-day course of ceftriaxone 250 mg IM daily as an outpatient beginning at week 28 of pregnancy. The patient tolerated both courses without any adverse events. Initial syphilis RPR titer was 1:64 at week 8; the RPR titer had fallen to 1:16 by the end of gestational week 32, indicating successful maternal treatment, with a 4-fold decrease in titer. She delivered at week 39.4; the baby had a positive syphilis screen (EIA) but negative RPR on day 1 of life. On day 2 of life, lumbar puncture was performed per the guidelines of the American Academy of Pediatrics (AAP) due to the mother's treatment with a regimen other than penicillin (11). The baby had a normal cerebrospinal fluid (CSF) profile with white blood cell (WBC) count <15 per mm<sup>3</sup>, protein of 52 mg/dL and no clinical signs of CS as well as normal roentgenography of the long bones. The baby was treated with 1 dose of benzathine penicillin (50,000 units/kg) according to AAP guidelines. At two-month follow-up, the child's RPR remained negative while syphilis EIA remained positive. Serology was expected to turn negative after washout of maternal antibodies.

## 3. Discussion

The regimen chosen for the patient was based on prior experiential treatment of early syphilis for pregnant patients with penicillin allergy to assess the efficacy of ceftriaxone to prevent CS: 8 HIV-negative pregnant women with early syphilis infection and skin-test-confirmed penicillin allergy (but without cephalosporin allergy) received either a 7- or 10-day course of ceftriaxone 250 mg IM (gestational age 4–17 weeks) followed by another 7–10-day course of ceftriaxone 250 mg IM at 28 weeks based on primary- or secondary-stage syphilis at initial diagnosis (5). The major limitation in this case was the dose, frequency, and duration of needed ceftriaxone therapy to prevent CS. In this patient, the first course was given parenterally to allow for inpatient monitoring. The strength that this case represents is the multidisciplinary approach between infectious diseases, obstetrics, and pediatrics to prevent CS. The patient felt at ease with the treatment offered and understood the risk of CS due to limited therapeutic options. She gave informed consent at all steps of her treatment, including publication of this case report.

Congenital syphilis is diagnosed in live-born infants by reactive RPR

testing from blood, findings on physical exam, radiographs, CSF analysis, or presumptively in infants born to mothers with untreated or inadequately treated syphilis (live-born or stillborn). Normal CSF analysis in neonates ≤30 days of age is defined as a WBC ≤ 15 per mm<sup>3</sup> or protein <120 mg/dL; for infants >30 days of age these values are WBC ≤ 5 per mm<sup>3</sup> or protein <40 mg/dL.

Although there is currently very little data on the use of cephalosporins in patients who have experienced severe delayed allergies like SJS with the use of penicillin for any cause, ceftriaxone has structurally dissimilar side-chains from penicillins and has been shown to have little or no cross-reactivity in the setting of immediate penicillin allergies (12,13). Lin et al. reported a case series of severe cutaneous adverse reactions (SCAR), including SJS, with penicillins and cephalosporins; among the seven patients challenged with a different beta-lactam class, 86% tolerated the course without event, and only one patient with a cefadroxil SCAR developed a reaction to ampicillin, which has a similar side-chain, in the form of a maculopapular rash (14).

Ceftriaxone has been used effectively to treat neurosyphilis as it crosses the blood–brain barrier (8,14–17); it also crosses the placenta and is safe for the fetus (18). Pharmacokinetic studies demonstrate the minimal inhibitory concentration (MIC) of ceftriaxone for *T. pallidum* is 0.0006 micrograms/ml (18) with excellent levels achieved in maternal serum after 1 g parenteral dose (peak 138 micrograms/ml) and is treponemocidal; fetal serum and amniotic fluid levels are 10–20% of maternal levels, which is still well above the MIC for *T. pallidum* (18,19).

## 4. Conclusion

We propose that, for pregnant patients with perinatal syphilis with a penicillin allergy preventing desensitization, ceftriaxone be used as an effective therapy to prevent congenital syphilis. We strongly suggest that the AAP and the CDC guidelines consider the use of ceftriaxone as a first-line treatment alternative to benzathine penicillin G to prevent congenital syphilis. More studies are needed to understand the optimal dosing and route of administration of ceftriaxone.

## Contributors

Meredith Coyle contributed to the inpatient and outpatient care of the mother as well as drafting and editing the manuscript.

Shawn Depcinski contributed to care of the mother while an outpatient, as well as drafting and editing the manuscript.

Muthayipalayam Thirumoorthi contributed to the inpatient and outpatient care of the neonate, as well as editing the manuscript.

All authors approved the final manuscript.

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## Patient consent

Written informed consent was obtained from the patient for the publication of this case report.

## Provenance and peer review

This article was not commissioned and was peer reviewed.

## Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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