ASTDA Position Paper: Alternatives to Benzathine Penicillin G for the Treatment of Syphilis During Pregnancy

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The 2021 Centers for Disease Control and Prevention (CDC) Sexually Transmitted Infections (STI) Treatment Guidelines recommend penicillin as the only effective antimicrobial therapy for pregnant patients for all stages of syphilis.[1] Consequently, there are no recommended alternatives to benzathine penicillin G (BPG) for the treatment of early- and late-stage syphilis in pregnancy. Pregnant individuals with a penicillin allergy must undergo desensitization. Shortages of BPG, like the one first reported in April 2023, threaten effective treatment of syphilis in pregnant persons and prevention of congenital syphilis.[2]

Treponema pallidum divides relatively slowly—once every 30 to 33 hours.[3,4] Given this replication rate, it has been suggested that effective treatment of early syphilis requires maintenance of a minimal serum concentration of 0.03 IU of penicillin/mL (0.018 μg/mL) for 7 to 10 days[5,6]—achievable in most nonpregnant individuals with a single intramuscular (IM) dose of BPG.[6,7] Lower serum levels of penicillin might still be effective, but data are sparse.[7,8] Long clinical experience supports the efficacy of BPG to treat pregnant patients, although in one small study of pregnant people getting BPG, the mean (±standard error) penicillin concentration in maternal serum declined from 0.14 ± 0.04 μg/mL 1 day after injection to 0.08 ± 0.06 μg/mL 7 days after injection. The proportion of individuals with a penicillin concentration at or above 0.018 μg/mL in the maternal serum declined significantly from day 1 to day 7 (90% at day 1 [9 of 10], 60% at days 2–3 [3 of 5], and 40% at day 7 [4 of 10]; $P = 0.03$).[7] Guidelines recommend the same single-dose BPG regimen to treat early syphilis in pregnant as in nonpregnant individuals. Based on limited data, some clinicians may treat pregnant people with early syphilis with a second dose of BPG, which is allowable though not mandated by guidelines.[1] Robust data to define the optimal duration of therapy for late latent syphilis are lacking; however, guidelines in both pregnant and nonpregnant individuals recommend 3 doses of BPG, given a week apart, to achieve a total duration of approximately 21 to 28 days of treatment.[1]

In assessing possible alternatives to BPG to treat syphilis in pregnant persons, it is important to remember that during pregnancy, anatomic and physiologic changes impact drug pharmacokinetics. Increased intravascular volume (up to 50% in the third trimester) and decreased plasma protein concentrations affect the volume of distribution of drugs. Blood flow to various organs, including the kidneys, increases. This is relevant for medications which are primarily renally excreted. Changes to drug-metabolizing enzymes occur throughout pregnancy resulting in supratherapeutic or subtherapeutic drug concentrations.[9–11] In addition, decreased absorption because of nausea and vomiting starting in the first trimester and delayed gastric emptying can impact drug concentrations.[12] Finally, the process of labor can also result in vomiting, delayed gastric emptying, fluid shifts, and rapid changes in hormone profiles, all of which can affect drug concentrations.[12] Understanding the changes in pharmacokinetic (PK) parameters and the ability to reach appropriate drug concentrations is essential to creating evidence-based dosing regimens during pregnancy.[10] Safety concerns for both the pregnant person and the fetus are of paramount importance and must be considered carefully.

The latest shortage of BPG is neither the first nor likely to be the last.[13] Clinicians worldwide routinely face BPG shortages. Inadequate treatment of syphilis in pregnancy not only endangers the pregnant person but also can lead to congenital infection in 50% to 70% of pregnancies with early and 15% of pregnancies with late syphilis—with often devastating consequences.[14]

The National Institutes of Health convened a workshop to assess alternative agents to treat syphilis, including in pregnant persons.[15] Separately, an expert working group assembled by the American Sexually Transmitted Diseases Association (ASTDA) reviewed the literature for data on alternative agents to BPG for the treatment of syphilis during pregnancy, as well as data on the pharmacokinetics/pharmacodynamics (PK/PD) of these medications to inform what agents may be considered in extreme circumstances. This document is not intended as a formal clinical practice guideline, nor is it intended to replace clinical decision making or supersede existing national guidelines. Rather, its goal is to provide pragmatic information to help inform clinician decision making in an important area with limited information. Finally, none of the alternative agents reviewed in this document should be considered for use unless BPG cannot be obtained. A reported allergy to penicillin always requires desensitization and use of BPG in pregnant individuals.

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Conflict of Interest and Sources of Funding: S.T. receives royalties from UpToDate and participates in research supported by in-kind donation of test kits by Hologic to her institution. K.G. receives royalties from UpToDate. H.R. was site PI on a Hologic grant to her institution for surveillance of *Mycoplasma genitalium* (ended 2023). Z.W. receives royalties from UpToDate, DynaMed, and Elsevier. All other authors declare no conflicts of interest.

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Received for publication August 26, 2024, and accepted November 14, 2024.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (http://www.stdjournal.com).

DOI: 10.1097/OLQ.0000000000002108

METHODS

Based on expert consensus and review of the literature, a working group including representatives from infectious diseases, pharmacology, gynecology and obstetrics, and pediatrics identified alternative regimens to BPG for which there is known efficacy and are available in the United States for syphilis treatment in nonpregnant persons. The group then performed focused searches to identify data on the use of each regimen in pregnant persons and on the PK of each drug during pregnancy using multiple search words in the English literature (Supplemental Materials: Literature Searches, http://links.lww.com/OLQ/B159). Relevant publications were abstracted into tables (Supplemental Tables 1–6, http://links.lww.com/OLQ/B159), and the implications for treatment of syphilis in pregnancy were summarized. The publication was reviewed by the entire ASTDA board and approved with a majority vote.

RESULTS

Intravenous Penicillin

Penicillin is considered safe for use during pregnancy[16–19] and exhibits antibacterial effects based on the percentage of time that free drug concentrations remain above the organism minimum inhibitory concentration (MIC; $\%fT > \text{MIC}$). Optimizing the time-dependent activity of β-lactams such as penicillin relies on consistently maintaining circulating drug concentrations over the duration of the dosing interval, ideally in a range of at least 40% to 70% $fT > \text{MIC}$.[20] Because of increased plasma volume and creatinine clearance during the second and third trimesters of pregnancy, serum penicillin concentrations may be decreased by as much as 50%. This may require increased dosage and/or frequency of dosing to achieve similar antimicrobial exposure to nonpregnant adults.[21–23] There is limited information on PK changes of intravenous (IV) penicillin during pregnancy, and much of the available PK data come from studies on group B streptococcus (GBS) prophylaxis and IV penicillin G during labor and delivery. Johnson et al.[24] determined the optimal dosing interval for IV penicillin for GBS prophylaxis. Penicillin G given at a dose of 1 million units IV resulted in a C_{max} of 67 μg/mL, which was over the MIC of GBS of 0.12 μg/mL. The authors concluded that standard 4-hour dosing intervals were appropriate. A pregnant cohort who received a 5-million-unit loading dose followed by 2.5 million units every 4 hours (standard dosing for GBS prophylaxis) had an average cord blood level of 2.4 μg/mL (range, 0.5–35 μg/mL). Cord blood concentrations were higher than the MICs for GBS.[25] An additional study[26] compared penicillin concentrations in obese and nonobese pregnant people. The maternal serum penicillin concentrations were not different, but the cord blood penicillin concentrations were up to 60% lower in the obese cohort. However, this did not impact outcomes as the concentration still exceeded the MICs for GBS.[26] Based on the available data, no change in dosing for IV penicillin G is recommended by the CDC STI guidelines during pregnancy.[1]

For neurosyphilis, the CDC recommends IV penicillin G 18 to 24 million units every 24 hours for 10 to 14 days in both pregnant and nonpregnant adults. It can be given as a continuous infusion or divided into 3 to 4 million units every 4 hours.[1] Limited published data exist on the use of IV penicillin G for stages of syphilis other than neurosyphilis in pregnancy (Supplemental Table 1, http://links.lww.com/OLQ/B159). A case report from Japan described 8 pregnant people with early (n = 2) and late latent (n = 6) syphilis who received IV penicillin, amoxicillin, or IV penicillin plus amoxicillin for treatment. Four of the 8 received only IV penicillin G; an additional 2 received a combination of IV penicillin G and amoxicillin.[27] In those treated with penicillin, 3 of the 6 demonstrated an adequate serological response and were considered effectively treated. In 1 patient, the starting rapid plasma reagin (RPR) was very low, so a serologic response was not observed. Two of the women did not have RPR titer decreases despite treatment. There were no cases of congenital syphilis reported in any of the women who received antibiotic therapy. As BPG is not available in Japan, the authors recommended a penicillin dose of 24 million units IV for 14 to 21 days.[27]

The optimal dosing for IV penicillin G to treat stages other than neurosyphilis in pregnancy is unclear. For a single IM dose of 2.4 million units of BPG as comparison, reported serum concentrations appear to range between 0.015 and 0.375 μg/mL at 6 to 9 days after administration, decreasing to approximately 0 to 0.015 μg/mL by days 13 to 16 in nonpregnant adult patients.[22–25] As aforementioned, serum penicillin concentrations after BPG administration may be somewhat reduced in pregnant patients. In a single cohort of 25 pregnant patients, reported mean serum was 0.08 (SE, ±0.02) μg/mL by day 7 after BPG.[7] Serum levels of penicillin after continuous or intermittent administration of IV penicillin G have variable reported range. One study of patients who received 12 million units/d continuous infusion had median plasma concentration of 13.7 μg/mL (range, 5.2–53.6 μg/mL).[28] Patients who received a similar daily dose (10.5–13.5 million units/d) divided every 4 hours had serum penicillin levels ranging from 0.26 to 100 μg/mL.[29] An approximate regimen of 19.2 million units/d reported an average serum level of 16 μg/mL.[30] Thus, with both intermittent administration and continuous infusion, serum levels of penicillin G after IV administration likely far exceed serum concentrations achieved by IM BPG at doses less than the 18 to 24 million units/d used for neurosyphilis. Although lower doses of IV penicillin might be adequate, the exact dose that would achieve similar serum drug concentrations to 2.4 million units of IM BPG administered over 7 days has not been established. The duration of therapy is also not clear. To best mirror the coverage of current IM BPG therapy regimens,[30] it is anticipated that 7 to 10 days and 21 to 28 days of IV penicillin would be necessary to treat early syphilis and late latent syphilis, respectively.

Conclusions: Although it seems reasonable to assume that IV penicillin G would be a safe and efficacious alternative if BPG is unavailable for early and late latent stages of syphilis during pregnancy, the optimal dosing is not known. Neurosyphilis dosing of IV penicillin should be adequate to treat other stages of syphilis. A duration of 7 to 10 days for early syphilis and 21 to 28 days for late syphilis would likely be adequate, although it might far exceed necessary dosing. The challenges of giving IV medications for these extended durations, which would require either inpatient care or home health for outpatient IV administration, limit the utility of IV penicillin G for non-neurosyphilis stages during pregnancy.

IV or IM Ceftriaxone

Ceftriaxone is widely distributed in tissues and body fluids.[11] Similar to other β-lactam agents, its primary efficacy parameter is contingent on the duration of maintained drug concentrations above the organism MIC ($\%fT > \text{MIC}$). Limited data suggest that ceftriaxone pharmacokinetics are similar in pregnant and nonpregnant patients.[11,31s] The lack of impact of pregnancy on the pharmacokinetics of ceftriaxone (in contrast to some other antibiotics) may be, in part, due to a substantial proportion of the drug being eliminated by nonrenal mechanisms.[11] Elimination of ceftriaxone may be slower in pregnant versus nonpregnant individuals, but these data are derived from a small number of individuals undergoing cesarean section, so no definitive conclusions can be drawn.[32s] Two studies performed in women undergoing cesarean

sections reported substantially lower concentrations of ceftriaxone in maternal serum as compared with amniotic fluid or placental tissue, but these samples were taken shortly after administration and were postpartum.[32s,33s] Current CDC guidelines recommend ceftriaxone 1 g daily either IM or IV for 10 days as an alternative for primary and secondary syphilis or ceftriaxone 1 to 2 g daily either IM or IV for 10 to 14 days as an alternative for neurosyphilis in nonpregnant adults; it is not mentioned as an option for latent syphilis.[1] Ceftriaxone is generally considered safe in pregnancy.[1]

There are limited data on the use of ceftriaxone in pregnant patients with syphilis (Supplemental Table 2, http://links.lww.com/OLQ/B159). Ceftriaxone was used in pregnant patients with syphilis in 14 individual case reports.[34s–37s] Thirteen cases had early latent, primary, or secondary syphilis[35s–37s]; syphilis stage was not specified in 1 patient. Two patients were given ceftriaxone after receiving penicillin or amoxicillin.[34s,36s] Ceftriaxone regimens varied. Eleven patients received ceftriaxone 250 mg IM daily for 7 days for primary and 10 days for secondary syphilis; in 8 cases, the regimen was repeated at 28 weeks' gestation. One individual received ceftriaxone 2 g daily for 8 days (after receiving amoxicillin and probenecid).[36s] Another received ceftriaxone 1 g IV daily for 10 days, followed by a second 10-day course of ceftriaxone 250 mg IM daily at week 28.[35s] One individual received 2 weeks of IV ceftriaxone, but the dose was not specified.[34s] None of the infants were diagnosed with congenital syphilis after use of ceftriaxone, but regimens differed, and long-term follow-up was often lacking. Finally, a case series from Latvia reported use of ceftriaxone in 79 pregnant participants with early syphilis (26 with secondary and 53 with early latent) followed over 12 months. There were significant limitations to this study, which make interpretation difficult.[38s] Those with secondary syphilis were given 500 mg of IM ceftriaxone for 10 days, but the exact regimen given for early latent syphilis was unclear. Although all of those with secondary syphilis had resolution of their symptoms and no clinical relapses were reported, serological outcomes involved nonstandard definitions including serologic reactions being considered "negative" if the "TPHA antibody titer had declined by half after 12 months post treatment." Unfortunately, no information on pregnancy outcomes and congenital syphilis was provided.[38s] There are no data on the use of ceftriaxone for stages other than early syphilis.

Conclusions: Although ceftriaxone may be an option to treat pregnant persons with syphilis, robust pharmacologic and clinical data are lacking. However, given its documented safety profile and its efficacy in nonpregnant individuals, it may be considered as an option in pregnancy if IM and IV penicillin are unavailable. The optimal dose and duration of ceftriaxone use during pregnancy are not defined. For pregnant individuals with primary or secondary syphilis, the recommended regimen for nonpregnant persons (1 g daily either IM or IV for 10 days for early syphilis) might be considered, but both patient and provider should be aware of the uncertainties and limitations of the data. The optimal duration of ceftriaxone therapy for late latent syphilis is not clear but, based on the duration of recommendations for penicillin, would likely be 21 to 28 days.

Tetracyclines

The antimicrobial family of tetracyclines, first isolated in 1948, inhibits protein synthesis by binding to the 30S subunit of the ribosome. The second generation of tetracyclines, doxycycline and minocycline, is better tolerated, has a longer half-life and excellent bioavailability, is less expensive, and has broad spectrum activity. Doxycycline in particular exhibits a prolonged serum half-life of approximately 12 to 16 hours, largely due to its significant existence in a protein-bound state (82%–93%) in circulating blood.[39s] Like many other pharmaceutical agents, doxycycline is also a substrate of CYP3A4 hepatic enzymes and has been observed to have reduced serum concentrations in the presence of enzymatic inducers.[40s] Renal excretion of doxycycline accounts for approximately 30% to 65% of an orally administered dose and occurs solely via glomerular filtration. Remaining drug is otherwise typically eliminated via the feces, the degree of which increases in magnitude in the presence of renal impairment. Thus, despite reduced urinary clearance in renal impairment, avoidance of drug accumulation is observed due to a compensatory increase in fecal elimination when glomerular filtration is compromised.[41s,42s]

Doxycycline has been used for the treatment of early- and late-stage syphilis in nonpregnant individuals who are unable to take penicillin, and in small studies, it has been found to have similar efficacy to penicillin-based regimens.[1,43s–47s] The CDC 2021 STI Treatment Guidelines recognize the limitations of current data but support the use of doxycycline (100 mg orally twice daily for 14–28 days, depending on the stage of disease) in *nonpregnant* individuals with a penicillin allergy.[1] Doxycycline is recommended by the CDC as the treatment of choice in nonpregnant patients when BPG shortage requires selective treatment for patients likely to be compliant with a 2- to 4-week treatment regimen.[48s]

When reviewing doxycycline as an alternative regimen for the treatment of syphilis during pregnancy, however, there are several considerations. In utero exposures to first-generation tetracyclines were associated with congenital anomalies, transient bone growth development abnormalities, teeth discoloration, and hepatotoxicity.[49s] The Food and Drug Administration classifies doxycycline as category D. It has been avoided in both pregnant persons and children based on reports in the 1950s of side effects secondary to early-generation tetracycline such as tooth discoloration (reviewed in Briggs et al.[50s]). Doxycycline is currently first-line and/or recommended treatment in children of all ages for certain diagnoses such as Rocky Mountain spotted fever and Lyme borreliosis where effective alternate regimens are limited.[51s] Compared with tetracycline, doxycycline binds calcium less avidly (reviewed in Cross et al.[49s]). Other potential adverse outcomes such as spontaneous abortion and atrial and ventricular septal defects in the infant have been noted in some studies of tetracyclines[52s,53s] but not others (reviewed in Briggs et al.,[50s] Cross et al.,[49s], Wormser et al.[54s]). Recent systematic reviews have not found clear associations with these outcomes. There were no specific patterns of adverse maternal, pregnancy, and fetal/neonatal outcomes identified; however, data were limited.[49s,55s] Although this is at least somewhat reassuring, more data are needed to better elucidate the safety or risks of doxycycline in pregnancy.

There are no pharmacometrics data on doxycycline to inform optimal dosing during pregnancy. Given the pharmaceutical profile of doxycycline outlined above, it is likely that its pharmacokinetics would be impacted by metabolic changes known to occur in pregnancy. Dilutional reductions in albumin, induction of CYP3A4 metabolism, and increased glomerular filtration are all anticipated to potentially increase doxycycline clearance and reduce serum levels in pregnancy, although to an undetermined degree of magnitude. Consequently, optimal dosing regimens of doxycycline in pregnancy are unknown. Standard adult nonpregnant dosing of doxycycline has been recommend in the treatment of other infections in pregnancy.[56s]

There are only a few case reports and one small case series evaluating the use of any tetracycline in pregnancy (Supplemental Table 3, http://links.lww.com/OLQ/B159). A case series detailed 12 pregnant patients in the second trimester with secondary syphilis who received achromycin, a first-generation tetracycline, for 14 days. There were no treatment failures and no neonates diagnosed with congenital syphilis.[57s] One case report described a

pregnant patient receiving tetracycline for 14 days for a urinary tract infection and who, 3 weeks later, at delivery, was diagnosed with syphilis and required penicillin for a "treatment failure." The infant was diagnosed with congenital syphilis at 10 weeks of life. As the tetracycline was given late during pregnancy and it was unknown when the pregnant person contracted syphilis, conclusions are limited.[58s] Finally, there was a recent case report of a pregnant patient who failed azithromycin treatment for syphilis at 10 weeks' gestation then received a 2-week course of doxycycline at 17 weeks' gestation with clinical and laboratory responses. The patient did receive another course of azithromycin in the third trimester for bronchitis, but the authors stated that the clinical and laboratory evidence of syphilis had improved after the doxycycline.[59s]

Conclusions: Tetracyclines as a category are not recommended for use in pregnancy. Doxycycline might be considered as an alternative therapy for the treatment of syphilis in pregnancy *only* if penicillin or ceftriaxone is unavailable and in conjunction with patient-provider shared decision making with careful discussion of potential risks and uncertainties. Given that the optimal dosing of doxycycline for the treatment of syphilis in pregnancy is unknown, standard stage-appropriate nonpregnant adult dosing and duration may be considered; however, patient and provider should be aware of the uncertainties.

Amoxicillin

Studies that examine PK data of amoxicillin to treat infections have focused on either amoxicillin along with probenecid to treat neurosyphilis[60s] or one oral (PO) dose of amoxicillin to multiple doses of IV ampicillin to treat infections at the time of birth. In nonpregnant adults, the half-life of amoxicillin is approximately 61.3 minutes and is estimated to have 60% of drug eliminated in the urine within 6 to 8 hours. Prior studies have observed findings of increased amoxicillin clearance of 86.4% to 123.3% and shorter half-lives by 18.8% to 31.3% in pregnancy.[61s–64s] Modeling studies have indicated that more frequent dosing of amoxicillin may be needed in later trimesters of pregnancy based on PK data from 16 subjects.[61s] Other studies have been conducted at the time of delivery with findings from one study indicating that a single dose of amoxicillin 500 mg results in significantly lower levels of amoxicillin in placental and fetal tissue than in maternal tissue[65s] demonstrating that multiple doses and higher doses may be needed to reach appropriate levels in fetal tissues. Identification of optimal amoxicillin dosing in pregnancy is further confounded by the lack of availability of dedicated pharmacometric data, where much of the literature from outside of the United States report findings utilizing IV amoxicillin rather than oral (which demonstrates approximately 75% bioavailability).[66s]

Data are limited for the use of oral amoxicillin with or without probenecid as an antimicrobial agent to treat syphilis in pregnant patients (Supp. Table 4, http://links.lww.com/OLQ/B159). In Japan, where benzathine penicillin IM is not available, standard of care is to hospitalize the patient and administer IV penicillin for treatment of syphilis.[27,67s] When patients cannot be hospitalized, Japanese guidelines recommend oral amoxicillin or ampicillin with dosing of 1500 mg/d (i.e., 500 mg 3×/d) for 2 to 4 weeks for primary syphilis, 4 to 8 weeks for secondary syphilis, and 8 to 12 weeks for tertiary or later-stage syphilis in pregnant patients.[67s] A total of 85 cases have been reported where amoxicillin or ampicillin was used (at least partially) to treat syphilis in pregnancy.[27,36s,67s] Thirty-three early syphilis cases treated with amoxicillin or ampicillin with or without probenecid resulted in no infants born with congenital syphilis. Fifty-two late syphilis cases treated with amoxicillin (41 cases) or ampicillin (11 cases) resulted in 15 infants with congenital syphilis. At least 5 additional cases were lost to follow-up.[67s] All of the reported infants with CS (N = 15) were from pregnant persons with late syphilis treated with amoxicillin (1500 mg/d) as reported in a single study.[67s] The limited sample included people with and without responding RPR titers and variable follow-up, but all infants were serologically tested and had a normal physical examination.

Conclusions: Amoxicillin or amoxicillin plus probenecid is not a recommended treatment regimen for syphilis in nonpregnant patients in the United States. Data on its use in pregnancy are limited. It is recommended as an alternative regimen in Japan. Although data are somewhat more encouraging for treatment of early syphilis in pregnancy, reported cases of congenital syphilis in mothers with late latent syphilis who were treated with this regimen are concerning. Amoxicillin or amoxicillin plus probenecid is therefore not a recommended treatment regimen for syphilis during pregnancy.

Cefixime

Cefixime is a third-generation oral cephalosporin whose prior historical use in the realm of STIs was primarily for the treatment of gonorrhea. Although cefixime is no longer recommended as a first-line treatment for gonorrhea, it remains an alternative regimen for gonorrhea.[1] There are limited data for the use of cefixime in the treatment of syphilis (Supplemental Table 5, http://links.lww.com/OLQ/B159). Stafylis et al.[68s] performed a randomized, open-label, noncomparative pilot study in 58 men and nonpregnant women with early syphilis, which evaluated the efficacy of cefixime 400 mg orally twice a day for 10 days. The per-protocol population treatment response was 87% in the cefixime arm and 93% in the penicillin arm. The intention-to-treat population treatment response was 56% in the cefixime arm and 81% in the penicillin arm. The limited sample size precluded a definitive assessment of its efficacy but suggested that this regimen could be considered for the treatment of early syphilis. Cefixime has been shown to have high transplacental transfer[69s] and is nonteratogenic. It is approximately 70% protein-bound with an estimated 15% to 21% renal elimination as parent drug, and although hepatic metabolism has been theorized to occur, no known metabolites have been identified.[70s] Current PK data for cefixime are in the context of currently Food and Drug Administration–labeled dosing strategies of 200 mg PO twice daily or 400 mg PO once daily, although a higher, 800-mg dose is recommended by the CDC for treatment of gonorrhea. In the future, if shown to be efficacious in nonpregnant adults initially and subsequently in pregnant persons, cefixime could be an attractive oral option during pregnancy.

Conclusions: Cefixime should not be used to treat pregnant persons with syphilis given the lack of data at this time.

Macrolides

There are no clinical trials or prospective observational studies assessing the efficacy of macrolides for the treatment of syphilis during pregnancy. There are limited PK data for macrolides in pregnancy (Supplemental Table 6, http://links.lww.com/OLQ/B159).[71s–74s] Available data do not allow an assessment of treponemicidal serum or tissue concentrations of macrolides in pregnant patients because of limitations in study designs. One study documented less than 5% transplacental transfer of erythromycin and azithromycin.[72s]

Macrolides are no longer recommended for the treatment of syphilis in the United States because of the widespread emergence of macrolide resistance in *T. pallidum*. There are multiple case reports of congenital syphilis developing after maternal treatment using various erythromycin formulations and azithromycin.[75s–80s]

Some of these failures may be due to macrolide resistance, but 2 case reports describe the occurrence of congenital syphilis in the offspring of mothers who demonstrated clinical and serological responses to macrolide therapy.[76s,79s] These cases suggest a mechanism of macrolide treatment failure in the fetus that is independent of macrolide resistance—perhaps as a result of the low transplacental transfer of these drugs.

Conclusions: Macrolides should not be used to treat pregnant patients with syphilis.

Use of BPG Alternatives and Implications for Infant Management

If a pregnant person receives any treatment of syphilis other than penicillin, management of the infant is notably impacted. The CDC defines "adequate treatment" of a pregnant person as "completion of a penicillin-based regimen, in accordance with CDC treatment guidelines, appropriate for stage of infection and initiated ≥4 weeks before delivery."[1] In addition to treatment with a nonpenicillin antibiotic, inadequate therapy includes treatment initiated <4 weeks before delivery, inappropriate dosing of penicillin for stage of syphilis, inadequate documentation of treatment for the pregnant person, and inadequate serological response to therapy (i.e., RPR titers do not decline at least 4-fold after treatment for the pregnant person). If adequate treatment is not received during pregnancy, the infant requires evaluations to assess the extent of disease and organ involvement. In addition to RPR, this may include complete blood count with differential and platelets, liver function testing, CSF analysis (including cell count, protein, and VDRL), auditory and ophthalmologic examination, long bone radiographs, and additional testing as warranted based on clinical findings (e.g., neuroimaging in the setting of abnormal neurologic examination). At the very least, infants will need close follow-up with serologic monitoring; at most, they may require a 10-day course of IV penicillin G.[81s]

Infants who have possible congenital syphilis with a negative workup, or infants with "less likely" or "unlikely" congenital syphilis per CDC guidelines, may need BPG and are thus impacted by BPG shortages. There are no acceptable BPG alternatives for these infants, apart perhaps from IV aqueous crystalline penicillin G or IM procaine penicillin G (which is no longer available in the United States) for 10 days, which is the regimen given to infants with confirmed congenital syphilis. Compared with BPG, this extended course is complicated and resource-intensive.

CONCLUSIONS

There are insufficient data to recommend any alternate regimen to BPG for the treatment of early syphilis or late latent syphilis during pregnancy. We emphasize that the CDC STI Treatment Guidelines (which recommend BPG for these individuals) should be followed. Macrolides, amoxicillin or amoxicillin plus probenecid, and cefixime cannot be recommended. The 2 regimens that might be considered in extreme circumstances in this population with proper patient-provider shared informed decision making are IV penicillin and ceftriaxone. Extrapolating from the neurosyphilis literature and known PK/PD of BPG, it is likely that IV penicillin at neurosyphilis dosing would be more than adequate for the treatment of uncomplicated syphilis during pregnancy, but the optimal dose is unclear. A duration of 10 days for early syphilis and 21 to 28 days for late latent syphilis may be considered. Per the CDC guidelines, IV or IM ceftriaxone can be considered in penicillin-allergic patients as an alternative regimen for neurosyphilis and early syphilis in nonpregnant adults. Although the PK/PD data are reasonable, there is a paucity of published data for its use during pregnancy. For pregnant individuals with early syphilis, the recommended regimen for nonpregnant persons (ceftriaxone 1 g daily either IM or IV for 10 days for early syphilis) might be considered; however, the optimal dose and duration of ceftriaxone use during pregnancy are not defined. The optimal duration of ceftriaxone therapy for late latent syphilis is not clear, but based on the duration recommendations for BPG, it would likely be 21 to 28 days. Relevant to consideration for IV penicillin as well as ceftriaxone, extended IV and IM courses are logistically very challenging limiting their use in many settings.

Doxycycline is a second-line option in nonpregnant patients for the treatment of syphilis. However, because of potential fetal toxicity concerns and the limited data on use and optimal dosing in pregnancy, doxycycline may be considered only in very limited circumstances for the treatment of syphilis in pregnancy in conjunction with a detailed discussion of risks and uncertainties for informed patient-provider shared decision making.

The paucity of data on alternatives to BPG in pregnancy is a critical issue that must be addressed. There are countries around the world that routinely use alternate agents to treat syphilis in pregnancy. We call on clinicians worldwide who have observational data on alternate agents to publish these data. We call on funding agencies to prioritize this issue. Although clinical trials are a complex undertaking, especially in this population, they are essential. Additional research to find viable alternatives to BPG for the treatment of syphilis in pregnancy is a critical unmet need.

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