PROVIDER HEALTH ADVISORY

Special Considerations for the Treatment of Syphilis in Non-Pregnant Persons

Guidance for using Alternative Therapies Amid Prolonged Bicillin® L-A Supply Shortage

Date: September 28, 2023
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The state of California continues to see significant increases in syphilis, including syphilis in pregnant persons and congenital syphilis in infants. Syphilis has also been increasing in SLO County.

This letter from the California Department of Public Health outlines guidance for using alternative therapies in non-pregnant persons for the treatment of syphilis. This guidance considers the ongoing medication shortage of long-acting penicillin G benzathine injectable suspension product (Bicillin® L-A)—now expected to last months into 2024.

For guidance on using alternative medications to treat non-pregnant persons with syphilis, please review this letter (see attached below).

State of California—Health and Human Services Agency
California Department of Public Health

TOMÁS J. ARAGÓN, MD, DrPH
Director and State Public Health Officer

GAVIN NEWSOM
Governor

September 12, 2023

Special Considerations for the Treatment of Syphilis using Alternative Therapies in Non-pregnant Persons

Dear Colleague,

In early June, the California Department of Public Health (CDPH) released a Health Advisory informing providers of **long-acting penicillin G benzathine injectable suspension product (Bicillin® L-A) shortages**, along with acceptable alternatives (e.g., doxycycline), recommendations for Bicillin® L-A prioritization (e.g., pregnant people & infants), and conservation guidance (e.g., non-Bicillin® L-A based antimicrobials for non-syphilis infectious diseases). Regrettably, updated estimates from the U.S. Food & Drug Administration indicate inadequate Bicillin® L-A supplies at least until the 2nd quarter of 2024 due to increased demand and limited manufacturing capacity.

In the setting of Bicillin® L-A supply shortages, CDPH would like to provide further guidance regarding the use of alternative syphilis treatment regimens for non-pregnant persons in unique situational and clinical case scenarios:

Combining the Use of Bicillin® L-A and Doxycycline:

Late latent syphilis or syphilis of unknown duration

Providers may be compelled to switch non-pregnant patients to doxycycline after receiving their first or second weekly injection (Bicillin® L-A 2.4 mu IM). Currently, there are no data supporting effective combination therapy. **Therefore, when using doxycycline following only one or two injections of Bicillin® L-A in the treatment of late or unknown duration syphilis, the safest and most conservative approach would be:**

- **Prescribe full 28 days of doxycycline 100mg BID following one or two injections of Bicillin® L-A**

CDPH is aware some providers may use less than 28 days of doxycycline after one or two doses of Bicillin® L-A, however currently there are no available data to support the following:

- Prescribing three weeks of doxycycline 100mg BID one week after a single injection of Bicillin® L-A
- Prescribing two weeks of doxycycline 100mg BID one week after two weekly injections of Bicillin® L-A

***If the above regimens are used, CDPH recommends getting more frequent serologies (RPR/VDRL titer) in follow up (i.e., every 3 months).**

Ceftriaxone:

Based on limited data, CDC 2021 STI Treatment Guidelines include ceftriaxone as an effective therapy option for the treatment of primary and secondary syphilis, and neurosyphilis. However, optimal dosing and duration have not been well established.

Primary and secondary syphilis

Available evidence to date suggests a 10-day regimen of ceftriaxone 1g IM/IV daily is "noninferior" to two weekly doses of Bicillin® L-A.[1] Notably, CDC recommends a *single* IM dose of Bicillin® L-A for primary and secondary syphilis, as evidence shows a second dose does not add benefit.[2] Despite pharmacologic studies showing ceftriaxone achieves necessary treponemacidal MIC levels (0.0006 micro gms/mL) at 1g daily, there are no data to support a shorter duration of therapy, such as a 7-day course. **Therefore, for an alternative treatment of primary and secondary syphilis, the safest and most conservative approach would be:**

- **Prescribe full 10 days of ceftriaxone 1 g IM or IV**

Neuro/ocular or otic syphilis:

CDC recommends aqueous crystalline penicillin G IV 3-4 mu every 4-6 hours for 10-14 days as the preferred treatment for neurosyphilis. However, lest this also becomes unavailable, and the fact CDC's recommended alternative treatment option for neurosyphilis, procaine penicillin IM, has been discontinued, CDC takes into account the use of ceftriaxone as an option based on limited evidence. Two case reports have found *ceftriaxone 1g daily for a total of 14 days* achieves significant decreases in both serum and cerebrospinal fluid IgG reactivity.[3,4] Additionally, a retrospective multicenter study concluded *ceftriaxone 2g for "at least 10 days"* provides an effective alternative compared to aqueous crystalline penicillin IV 3-4 mu every 4-6 hours for 10 days.[5,6] **Therefore, in the event of aqueous crystalline penicillin G IV shortages, and no available procaine penicillin G IM, an alternative approach to the treatment of neuro/ocular or otic syphilis would be:**

- **Prescribe at least 10 days ceftriaxone 2g daily IM or IV** -OR-
- **Prescribe at least 14 days ceftriaxone 1g daily IM or IV**

Follow-up:

All patients treated for primary and secondary syphilis, late latent syphilis or syphilis of unknown duration, and/or neurosyphilis, should receive routine clinical and serologic (i.e., RPR or VDRL titer) follow up at 6 and 12 months to confirm treatment efficacy. **Providers should consider more frequent clinical and serologic follow up (e.g., 3-month intervals) in patients who are treated with any of the above alternative medication modalities.**

Additionally, providers should consider prescribing doxycycline post-exposure prophylaxis (doxy-PEP) to prevent syphilis infections (and gonorrhea & chlamydia), which in turn reduces Bicillin® L-A demand and preserves current supplies.

Please reach out to stdcb@cdph.ca.gov if you have any questions about this guidance.

Sincerely,

Kathleen Jacobson, MD
Chief, STD Control Branch
California Department of Public Health

Resources:

- CDPH Health Advisory: Bicillin® L-A (Benzathine Penicillin G) Shortage
- FDA Bicillin® L-A shortage webpage
- CDC CDC - STD Treatment - Drug notices
- CDC Syphilis - STI Treatment Guidelines, 2021
- CDC Congenital Syphilis - STI Treatment Guidelines, 2021
- CDC Syphilis | Effects and Burden | Pregnancy
- FDA Ceftriaxone (Rocephin) Package Insert
- CDPH Doxy-PEP Recommendations for Prevention of STIs

References:

1. Cao Y *et al*. *A Multicenter Study Evaluating Ceftriaxone and Benzathine Penicillin G as Treatment Agents for Early Syphilis in Jiangsu, China*; *Clinical Infectious Diseases*, Volume 65, Issue 10, 15 Nov 2017;1683-1688. https://doi.org/10.1093/cid/cix611
2. Rolfs RT *et al*. *The Syphilis and HIV Study Group. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection*. N Engl J Med 1997;337:307–14. PMID:9235493 https://doi.org/10.1056/NEJM199707313370504
3. Hook EW 3rd, *et al*. *Ceftriaxone therapy for asymptomatic neurosyphilis. Case report and Western blot analysis of serum and cerebrospinal fluid IgG response to therapy.* Sex Transm Dis. 1986 Jul-Sep;13(3 Suppl):185-8. PMID: 3764632.
4. Shann S, Wilson J; *Treatment of neurosyphilis with ceftriaxone*. Case Report. Sexually Transmitted Infections 2003;79:415-416. Treatment of neurosyphilis with ceftriaxone (nih.gov)
5. Bettuzzi T *et al*. *Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: a retrospective multicentre study*. Lancet Infect Dis. 2021 Oct;21(10):1441-1447. doi: 10.1016/S1473-3099(20)30857-4. Epub 2021 May 26. Erratum in: Lancet Infect Dis. 2021 Aug 5; PMID: 34051142. DOI: 10.1016/s1473-3099(20)30857-4
6. Ceftriaxone for Neurosyphilis, *Clinical Infectious Diseases*, Volume 73, Issue 7, 1 October 2021, Pages i–ii, https://doi.org/10.1093/cid/ciab775