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**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 2<sup>nd</sup> 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3,4</sup> 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.<sup>5,6</sup> **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](mailto:stdcb@cdph.ca.gov) if you have any questions about this guidance.

Sincerely,



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#### 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](https://doi.org/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>