Treatment Intervals for Pregnant Patients with Syphilis of Late Latent or Unknown Duration: Clinical Recommendations for California Providers

During pregnancy, the only recommended treatment for late latent syphilis or syphilis of unknown duration is benzathine penicillin G (BPG, also known as Bicillin L-A), administered as 3 intramuscular (IM) doses of 2.4 million units (mu), each ideally given at 7-day intervals (for a total of 7.2 mu). If strict 7-day intervals are not possible, and there are too many or too few days between BPG injections, the full 3 dose treatment series may need to be restarted. This document shares California Department of Public Health (CDPH) clinical recommendations for managing cases when BPG dosage intervals are less or greater than 7 days when treating pregnant patients with syphilis of late latent/unknown duration syphilis. CDPH recommendations regarding BPG treatment intervals in non-pregnant patients are available separately.

CDPH recommends adhering to strict 7-day BPG treatment intervals when treating pregnant patients with syphilis of late latent/unknown duration.

To eradicate the bacteria that cause late-latent syphilis, a minimum serum penicillin concentration of 0.03 IU/ml (0.018 ug/ml) must be sustained over 21 days, and not be interrupted for more than 24-30 hours.[1] Among non-pregnant patients, pharmacologic data suggest that treatment intervals of 7-9 days between each 2.4 mu BPG injection are preferable to achieve uninterrupted serum concentrations at the desired level for the full 21-day treatment period.[2,3] In pregnancy, however, physiologic changes—such as increased blood volume, cardiac output, renal blood flow, creatinine clearance, and total body water, combined with decreased plasma protein concentrations—are likely to result in lower serum penicillin concentrations and fewer days of adequate penicillin coverage per BPG injection.[4] For these reasons, and because robust pharmacologic data are lacking among pregnant patients, CDPH recommends making every effort to adhere to strict 7-day BPG treatment intervals when treating pregnant patients with syphilis of late latent/unknown duration.

Based on an analysis of available California data, 6-8 day BPG treatment intervals (i.e., 7-day intervals plus or minus one day on either side) may be effective when strict 7-day intervals are not possible.

California data indicates that 6-8-day BPG treatment intervals are likely effective for the purposes of preventing congenital syphilis (CS) in cases where strict 7-day intervals are not possible. A prior study[5] used state STD surveillance data to identify mother/infant dyads in which pregnant patients with late latent syphilis or syphilis of unknown duration received either: (1) BPG dosed as three weekly IM injections at strict 7-day intervals, (2) BPG dosed as three weekly IM injections in which at least one interval was at 6-8-days, or (3) no/inadequate treatment. The authors found that the odds of CS in infants whose parents were treated at 6-8-day intervals were equivalent to those whose parents received treatment at strict 7-day intervals (odds ratio 1.0; 95 percent confidence interval 0.4-3.0). In contrast, infants born to pregnant patients with no/inadequate treatment in pregnancy had much higher odds of CS (odds ratio 9.8, 95 percent confidence interval 6.6-14.7).

Intervals longer than 8 days may be less effective in preventing CS; therefore, CDPH does not recommend this approach.

CDC 2021 STI treatment guidelines[6] for pregnant patients state that missed doses >9 days between BPG injections are not acceptable – thus implying that 9-day intervals may be acceptable. CDPH data, however, suggest 9-day intervals may be insufficient to prevent CS. A more recent California study[7] compared mother/infant dyads in which the mother had late latent syphilis or syphilis of unknown duration in pregnancy and received: (1) BPGx3 dosed at either 6-8-or 7-day intervals, (2) BPGx3 with at least one 9-day interval (and no intervals outside 6-9-days), or (3) no/inadequate treatment. In this analysis, odds of CS were nearly four-fold higher among dyads who received BPGx3 with a 9-day interval compared with those treated at 7- or 6-8-day intervals (Odds ratio 3.7, 95 percent confidence interval 1.2-11.6). While larger studies with higher statistical power are needed, these findings hint that BPG intervals longer than 8 days may be less effective in preventing CS. For this reason, CDPH does not recommend using 9-day BPG treatment intervals in pregnancy. If patients are treated in pregnancy with 9-day intervals, CDPH recommends re-treatment, ideally using 7-day intervals (with 6–8-day intervals being acceptable).

The following table summarizes CDPH STD Control Branch recommendations for BPG treatment intervals for syphilis of late latent/unknown duration in pregnancy.

Summary of BPG Treatment Intervals for the Treatment of Late Latent Syphilis or Syphilis of Unknown Duration in Pregnant Patients:

Time interval between BPG injections	Categorization	Notes
7 days (exactly)	Ideal	• Strict 7-day intervals are best for treatment of late latent syphilis or syphilis of unknown duration. • Every effort should be made to use 7-day intervals for pregnant patients.
6-8 days	Acceptable	• California data suggests that infants are no more likely to meet criteria for congenital syphilis if pregnant patients are treated at 6–8-day intervals compared to 7-day intervals.[5]
9 days	Not recommended in California, despite being potentially permissible in CDC guidelines[6]	• California data indicates 9-day intervals may be less effective in preventing congenital syphilis. • CDPH recommends re-treatment, ideally at 7-day intervals (with 6–8-day intervals being acceptable). • If providers opt for 9-day intervals, a full CS workup for the infant at birth may be recommended (including lumbar puncture, blood draw, and long bone X-rays) as well as treatment with either IM or intravenous penicillin.
>9 days	Inadequate	• Retreatment recommended ideally at 7-day intervals (with 6-8-day intervals being acceptable).

For questions regarding recommended syphilis treatment in pregnant or non-pregnant patients, please contact the CDPH STD Control Branch via email (stdcb@cdph.ca.gov) or phone (510-620-3400). Questions can also be submitted online to the STD Clinical Consultation Network (stdccn.org), run by the California Prevention Training Center (CAPTC) at the University of California San Francisco. Also see the California STI Treatment Guidelines Table for Adults and Adolescents.[8]

Disclaimer: These guidelines are intended to be used as an educational aid to help clinicians make informed decisions about patient care. The ultimate judgment regarding clinical management should be made by the healthcare provider in consultation with their patient, in light of clinical data presented by the patient and the diagnostic and treatment options available. Further, these guidelines are not intended to be regulatory and not intended to be used as the basis for any disciplinary action against the healthcare provider.

References:

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4. Nathan L, et al. Penicillin levels following the administration of benzathine penicillin G in pregnancy. Obstet Gynecol 1993; 82:338–42.
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6. Centers for Disease Control and Prevention. 2021 STI Treatment Guidelines – Syphilis during Pregnancy. Available at: Syphilis During Pregnancy - STI Treatment Guidelines (cdc.gov).
7. Johnson KA, et al. Higher odds of congenital syphilis with 9 vs 7-day prenatal treatment intervals for late syphilis. Oral abstract presentation at: CROI 2025. 2025 March 11; San Francisco, CA.
8. CDPH STD Control Branch. California STI Treatment Guidelines Table for Adults and Adolescents. Available at: California STI Treatment Guidelines.