What are appropriate treatment intervals for late latent syphilis or syphilis of unknown duration in non-pregnant people?

For the treatment of late latent syphilis or syphilis of unknown duration, both the Centers for Disease Control and Prevention (CDC) and California Department of Public Health (CDPH) STD Control Branch recommend treatment with intramuscular (IM) benzathine penicillin G (BPG, also known as Bicillin L-A), administered as 3 doses of 2.4 million units (mu) each at 1-week intervals for a total of 7.2 mu. Ideally, the three weekly BPG injections would be given at strict 7-day intervals. When this is not possible, ambiguity exists as to how many days between injections is acceptable without having to restart the full 3-dose treatment series.

It is generally thought that treatment of late latent syphilis or syphilis of unknown duration requires a minimum serum penicillin concentration of at least 0.03 IU/ml (0.018 ug/ml) sustained over 21 days to eradicate the bacteria (or treponemes) that cause syphilis.[1] Among non-pregnant people, 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] That said, penicillin concentrations below 0.03 IU/ml could be allowable if not sustained for more than 24-30 hours.[1] Thus, BPG treatment intervals of 6-10 days are also likely acceptable. Based on clinical experience, the CDC 2021 STI treatment guidelines[4] state that intervals of up to 10-14 days between BPG doses may also be permissible in non-pregnant patients, although less evidence supports these longer treatment intervals.

CDPH recommends making every effort to ensure that non-pregnant patients with late-latent syphilis or syphilis of unknown duration are treated with BPG using intervals as close to 7 days as possible (with 6–10-day intervals being acceptable) to maximize the chances of syphilis eradication. **Since it can sometimes be challenging to ensure adequate treatment in cases of late latent or unknown duration syphilis, CDPH recommends the following (summarized in the table below):**

Summary of BPG Treatment Intervals for Treatment of Late Latent Syphilis or Syphilis of Unknown Duration in Non-Pregnant People		
Time interval between BPG injections	**Categorization**	**Notes**
7 days (exactly)	Gold Standard	Strict 7-day intervals are considered the "gold standard" for treatment of late latent syphilis or syphilis of unknown duration
7-9 days	Preferred (if 7 days not feasible)	Pharmacologic data suggest this interval allows for uninterrupted penicillin concentrations over a 21-day period
6-10 days	Acceptable	This interval may have penicillin concentrations below 0.03 IU/ml (0.18 ug/ml), but for less than 30 hours
11-14 days	May be permissible per CDC guidelines based on clinical experience[4]	Penicillin concentrations may fall below desired levels for more than 30 hours; consider re-treatment (see considerations below)
>14 days	Inadequate	Retreatment indicated

Discussion of potential treatment interval scenarios:

1. If a provider learns during the patient's 21-day treatment course that a non-pregnant patient has received BPG injections at treatment intervals outside of 6-10 days, consider restarting the treatment course with BPG given at the target treatment intervals (ideally 7 days, but not outside of 6-10 days between injections).

2. If a provider learns after the fact (but prior to 24 months post-treatment), that a non-pregnant patient with syphilis of late latent/unknown duration was previously treated at intervals between 11-14 (rather than 6-10) days, clinical judgement is required to determine next steps (in combination with shared clinical decision making).
    a. We first recommend starting with a repeat RPR, obtained at least 2 months post-treatment.
        i. If the RPR is stable (unchanged or within a two-fold change from prior, i.e. from 1:4 to 1:8) or lower than prior, and the patient reports no new syphilis exposures or signs/symptoms, it is permissible for clinicians to continue monitoring RPR titers without restarting the BPG treatment series.
        ii. If the RPR has risen by two-fold (i.e., from 1:4 to 1:8, or from 1:8 to 1:16), consider repeating an RPR in 1-2 months to ensure the RPR is not continuing to trend upward.
        iii. If the RPR is rising (increased by at least fourfold from prior, i.e., from 1:8 to 1:32) but the patient denies new exposures, the provider should perform a full neurologic exam (including assessment of vision and hearing).
            1. If any abnormalities are noted on the neurologic assessment, the patient should undergo a lumbar puncture and/or ophthalmology exam to further evaluate for neuro/ocular/otic syphilis.
            2. If there are no neurologic symptoms but the RPR has increased by fourfold or more from prior, the provider should restart the full 3-dose BPG series ideally at 7 (but not outside of 6-10) day intervals.

3. Clinical evaluation and retreatment with BPG at optimal intervals should also be considered if a patient remains asymptomatic but fails to achieve a fourfold decline in RPR (or VDRL) titers (i.e., from 1:32 to 1:8) by 24 months after treatment for late latent syphilis or syphilis of unknown duration. Such patients should be evaluated for HIV infection if their HIV status is unknown and should undergo complete neurologic, vision, and hearing exams since neuro, ocular, and otic syphilis are treated differently than other stages of syphilis. If any abnormalities are noted on neurologic exam, a CSF evaluation via lumbar puncture should be performed.

4. If a provider learns at any point that a non-pregnant patient with syphilis of late/unknown duration was treated with BPG at intervals exceeding 14 days, then their treatment should be considered inadequate, and the full 3-dose BPG treatment series should be restarted.

Other Considerations:

Ultimately, for non-pregnant patients who were treated at intervals outside of 6-10 (but not >14) days, the decision whether to retreat requires clinical judgement. Factors to take into consideration include: RPR titers and testing history, whether it is possible that the patient had early syphilis, whether it is possible that the patient is or could become pregnant, the patient's ability to follow-up with treatment,

and the risks of possible undertreatment. Since data is limited, the above factors and/or shared clinical decision making with the patient are recommended to determine the benefits and risks of offering retreatment versus monitoring RPR titers in individual patients.

For any questions regarding appropriate syphilis treatment in non-pregnant or pregnant patients, please contact the CDPH STD Control Branch via email (stdcb@cdph.ca.gov) or phone (510-620-3400). Also see the California STI Treatment Guidelines Table for Adults and Adolescents.[5]

References:

1. Ghanem K. Management of Adult Syphilis: Key Questions to Inform the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. CID 2015 Dec 15;61 Suppl 8:S818-36.
2. Frentz G, et al. Penicillin concentrations in blood and spinal fluid after a single intramuscular injection of penicillin G benzathine. Eur J Clin Microbiol 1984 Apr;3(2):147-9.
3. Hagdrup HK, et al. Penicillin concentrations in serum following weekly injections of benzathine penicillin G. Chemotherapy 1986;32(2):99-101.
4. Centers for Disease Control and Prevention. 2021 STI Treatment Guidelines – latent syphilis. Available at: https://www.cdc.gov/std/treatment-guidelines/latent-syphilis.htm.
5. California Department of Public Health STD Control Branch. California STI Treatment Guidelines Table for Adults and Adolescents. Available at: https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/California-STI-Treatment-Guidelines-for-Adults-and-Adolescents.pdf.