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How much penicillin is needed to treat early syphilis in people living with HIV?

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ABSTRACT A clinical decision report using:

Andrade R, Rodriguez-Barradas MC, Yasukawa K, Villarreal E, Ross M, Serpa JA. Single Dose Versus 3 Doses of Intramuscular Benzathine Penicillin for Early Syphilis in HIV: A Randomized Clinical Trial. *Clin Infect Dis*. 2017;64(6):759-764. https://doi.org/10.1093/cid/ciw862

to inform treatment of syphilis for a person living with HIV with multiple socioeconomic barriers to care.

Keywords: *syphillis, human immunodeficiency virus, HIV, penicillin doses*

Clinical-Social Context

Thomas Anderson [pseudonym] is a 26-year-old African American male, with past medical history significant for HIV infection, depression, and anxiety who presented to the Infectious Disease clinic for follow-up of HIV management and syphilis treatment. He had not taken his anti-retroviral medication bictegravir/emtricitabine/ tenofovir alafenamide for the last month due leaving town and leaving his medication behind. Two months prior to the current appointment, he visited the emergency department for tibial fracture and during work-up was found to have asymptomatic, early latent syphilis with reactive treponemal IgG/IgM and reactive rapid plasma regain (RPR) quant. He received one dose of benzathine penicillin G (BPG) during the emergency department visit, and one dose the next week, but did not follow up for his third dose, recommended by infectious disease (ID) consults at the time. The patient works three jobs and does not have stable housing. He finds it very difficult to make excuses to his employers for frequent visits to the physician and does not wish to disclose his HIV status. Additionally, he lacks secure transportation. Mr. Anderson would like to re-start his anti-retroviral medications, which he is able to afford with his medical insurance. He notes that he is currently engaged to a male partner and has had multiple other male sexual partners in the last year. He would like to know if the amount of BPG he received was sufficient to treat his syphilis infection.

Clinical Question

What dose of benzathine penicillin G is effective for treatment of early syphilis in people living with HIV (PLWH)?

Research Article

Andrade R, Rodriguez-Barradas MC, Yasukawa K, Villarreal E, Ross M, Serpa JA. Single Dose Versus 3 Doses of Intramuscular Benzathine Penicillin for Early Syphilis in HIV: A Randomized Clinical Trial. *Clin Infect Dis*. 2017;64(6):759-764. https://doi.org/10.1093/cid/ciw862 [1]

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Description of Related Literature

To first outline current treatment guidelines and definitions for syphilis, a search using the term "Syphilis treatment" was performed using the database PubMed. A 2014 systematic review by Clement et al. defined early syphilis as primary, secondary and/or early latent syphilis. Early latent syphilis includes asymptomatic patients who were infected with *Treponema pallidum* within the previous year. Most research has focused on efficacy of BPG for treatment of syphilis, but a small number of studies have also included doxycycline, ceftriaxone, and azithromycin as potential alternatives.[2] These alternative therapies are not included in the current clinical decision report. Treatment response to BPG is often monitored using nontreponemal serologic tests, such as the RPR tests. Generally, a 4-fold decline in nontreponemal titers signifies adequate treatment response.[2] Current CDC recommendations, include one dose of BPG for early syphilis,[3] regardless of HIV status, although this recommendation is not well reflected in clinical practice.[4]

To identify differences in treatment efficacy via varying doses of BPG, a search of PubMed was done using the following keywords: "penicillin doses" AND "syphilis" AND "HIV." This search yielded 46 results. Excluding results without full texts, 36 results remained. Upon review of the titles and abstracts, and works cited in these 36 results, four articles were available and directly compared syphilis treatment responses to one versus two or more doses of penicillin in people living with HIV.

Costa-Silva et al. conducted a retrospective cohort study in Portugal comparing treatment outcomes in PLWH, co-infected with syphilis who received a single dose vs three doses of BPG.[5] This study was excluded because of its retrospective, observational design. Additionally, the number of participants in the three-dose BPG cohort was more than twice the size of the single-dose BPG cohort, which made statistical evaluation and comparison more difficult.

Ganesan et al. conducted a retrospective cohort study using data from the US Military HIV Natural History Study (NHS).[6] They included participants followed by the NHS between 1986 and 2013, and compared treatment outcomes by monitoring a four-fold decline in RPR titers. This study was excluded because it employed an observational design with lack of randomization. Additionally, they included syphilis cases from the pre-highly active antiretroviral therapy (HAART) era, which may have had an influence on syphilis treatment outcomes.

Yang et al. completed a multicenter, prospective observational study in Taiwan between 2007 and 2012.[7] They did not randomly assign PLWH, co-infected with syphilis to one-dose vs. three-dose BPG treatment groups and relied on physicians for this clinical decision. This study was excluded because non-randomization may have resulted in bias between groups. It is possible physicians gave PLWH with greater risk for recurrent syphilis infection longer treatments courses of BPG. The study also did not distinguish between treatment failure and possible syphilis re-infection in their statistical analysis and follow up.

The Andrade et al. article is the first randomized controlled trial to compare the efficacy of single dose BPG with a three-dose regimen delivered at one-week intervals for syphilis treatment in PLWH.[1] The study found no improvement in syphilis serological outcomes between treatment groups and provides support for the CDC's recommendation for single dose BPG treatment in PLWH with early syphilis. This study was chosen for critical appraisal because of its robust randomized design, intention to treat (ITT) analysis, and stratification of results by syphilis stage, RPR titer, CD4 count, HAART use, and HIV RNA copies. Per the Strength of Recommendation Taxonomy (SORT) criteria, this study holds a Grade C Strength of Recommendation, based on disease-oriented outcomes.[8]

Critical Appraisal

The study by Andrade et. al is a prospective, randomized, open-label clinical trial comparing treatment efficacy of 3-dose vs single-dose of intramuscular BPG for early syphilis in PLWH in Houston, Texas. Per SORT criteria, this study is classified as Level 3 research.[8] Following diagnosis of syphilis by RPR test, study participants were randomized into single-dose or three-dose BPG groups and followed for 12 months with RPR titers drawn every three months. Following current international standards, treatment success was defined as a four-fold decrease in RPR titers.[1] A total of 64 PLWH underwent randomization. Initially, 35 were assigned to receive 2.4 million units of BPG on time and 29 were assigned to receive 2.4 million units of BPG three times. Baseline characteristics of study participants – such as age, sex, race/ ethnicity, CD4 counts, and HAART use – were similar between groups. All participants were included ITT analysis. A strength of this study is the randomized design, and comparable treatment groups. Unfortunately, the study is non-blinded, which creates opportunity for observer-expectancy bias. Second and third dose placebo injections for the single dose

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BPG group could have been used to blind participants and researchers from treatment group assignment. Any potential observer-expectancy bias was minimized in this study, however, through analysis of objective laboratory data for treatment outcome.

Inclusion criteria for the study were PLWH who had primary, secondary or early latent syphilis based on physical examination and positive RPR and *Treponema pallidum* particle agglutination (TP-PA) tests. PLWH who had late latent syphilis, defined as greater than 12 months since infection, documented penicillin allergy, and antibiotic use with significant activity against *Treponema pallidum* within two weeks prior to diagnosis were excluded from the study. These exclusion criteria are a strength of this research, eliminating potential confounding variables.

Intention to treat analysis showed no statistical difference between single-dose and three-dose BPG treatment groups (93% and 80% successful serologic response, respectively, with p=0.17. Statistical significance was set at $p < 0.05$). In the single-dose group, five PLWH were lost-to-follow-up (LTFU), and these participants were treated as treatment failures in ITT analysis. In comparison, two PLWH were LTFU in the three dose BPG group. When removing these LTFU participants in the per-protocol analysis, there was still no significant difference in outcome between treatment groups. Stratifying participants according to CD4 count at baseline, use of HAART at enrollment, HIV virologic suppression, RPR titer at enrollment, and syphilis stage did not produce significant differences in treatment outcomes between groups. This is a strong finding, especially considering clinicians' hesitancy in reducing BPG treatment for immunocompromised individuals.

The study had a small sample size and therefore lower statistical power. This is especially important to note for the early latent group of participants (n=18), whose success was 67% for single dose BPG and 100% for three-dose BPG. Although this was not a statistically significant difference (p=0.06), further research with more participants with early latent syphilis is needed to investigate this trend. It is possible the study was underpowered to detect small, but clinically significant differences in treatment outcomes between groups. This is especially pertinent to the patient presented in this article, Mr. Anderson, who presented with early latent syphilis. Additionally, this study failed to comment on number needed to treatment with three-dose and one-dose BPG regimen for one successful serologic response. The effect size is difficult to assess with given data.

Although the focus of this study was on serologic responsiveness to BPG treatment, there were no comments made on clinical improvement of participants. Another element of analysis that could have been added includes improvement in symptoms of syphilis such as resolution of rash, reduced fever, and reduced lymphadenopathy. Survey data may have added an important element of patient-oriented evidence to this research.

Overall, this Andrade et al. paper was representative of the demographics of PLWH in Detroit, both in terms of gender, race/ethnicity, and sexual practices (men who have sex with men). Houston, Texas and Detroit, Michigan have a comparable prevalence of syphilis[9] and HIV[10], and so results from this paper translate well to the case of Mr. Anderson. The greatest weaknesses of the research are the small sample size, non-blinding methodology, and lack of clinical data beyond serologic responsiveness to treatment.

Clinical Application

In the case of Thomas Anderson, a 26-year-old African American male, with past medical history of HIV, depression, and anxiety we were able to reassure him that he received adequate treatment for syphilis. At his current visit, we ordered another RPR quant to measure titers, and monitor for treatment response. The Andrade et al., paper is applicable to our patient because it was conducted in an urban environment in the United States, with a large portion of African American participants and men who have sex with men. This represents our patient, Mr. Anderson, and provides statistically significant evidence for treating early syphilis in PLWH with one dose, instead of three doses of BPG. Although our patient received two doses of penicillin, the study still provides evidence that Mr. Anderson did not require a third dose of BPG. This research helps confirm current CDC recommendations.

There are many PLWH not maintained in clinical care in the United States.[11] In Michigan, specifically, 71% of PLWH were retained in care and only 61% reached viral suppression in 2019.[12] Known barriers to care have included insufficiency social support[13], financial stress[14], stigma[15], and complicated lifelong medication treatments[16],

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especially in people with comorbid conditions.[17] Mr. Anderson was facing many of these barriers to care, and so it was important for his healthcare providers to consider socioeconomic determinants of health and streamline the number of required clinical visits for him. The ID clinic that Mr. Anderson attends also has a full-time social worker with links to community support resources and taxi vouchers. Thomas Anderson is now successfully re-engaged in care and has attended an additional follow-up appointment for HIV management.

New Knowledge Related to Clinical Decision Science

Many PLWH face comorbid infections, including syphilis, and it is extremely important to treat these infections as they arise. Equally important however, is consideration of patients' socioeconomic barriers and working with patients to come up with realistic treatment plans that are possible to follow. Although many physicians may be hesitant and prefer to play it safe with three doses of BPG treatment for syphilis in PLWH, the Andrade et al., study, as well as CDC guidelines advocate for reduced doses. The ID clinicians caring for Mr. Anderson opted for less than three doses of BPG, after he was unable to take enough time off work for further treatment. Clinical decision science considers social, economic, and biologic context of disease when creating treatment plans with patients. Each realm is important in improving outcomes and quality of life, especially for patients with chronic conditions such as HIV.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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