Critically Appraised Topic (CAT): Ceftriaxone or Doxycycline as an alternative to Penicillin to Treat Syphilis

Specific Care Question

In adolescent patients aged 12 – 18 years with syphilis, is ceftriaxone or doxycycline compared to benzathine penicillin G (BPG) as effective in resolving symptoms and infection?

Recommendation and Plain Language Summary

For patients with penicillin allergy or if BPG is unavailable, a **conditional** recommendation is made **for** the use of doxycycline as an alternative to BPG for the treatment of primary, secondary, or early latent syphilis in adolescent patients aged 12 – 18 years based on national guideline recommendations, indirect adult evidence, and clinical expertise.

This review was based on one systematic review and meta-analysis (4,485 participants)[1] and one retrospective cohort study (82 participants).[2] Compared with BPG, neither ceftriaxone nor doxycycline demonstrated a statistically significant difference in 12-month serological response. The certainty of the evidence was rated as very low due to indirectness arising from extrapolating findings from adult studies, risk of bias in the included studies, and methodological limitations of the systematic review. Because certainty is very low, this finding should be interpreted with caution and should not be treated as evidence of equivalent efficacy. Also, these studies do not consider the feasibility or acceptability of medication administration, which significantly affects adherence and patient confidentiality. A single intramuscular dose of BPG remains the first-line treatment across all age groups, including adolescents, because it provides reliable delivery without requiring subsequent doses. Ceftriaxone requires daily intramuscular or intravenous administration for 10-14 days, which may be impractical and costly for many patients. In contrast, doxycycline is administered orally at 100 mg twice daily for 14 days, allowing patients to complete treatment at home. This eliminates or decreases the need for repeated healthcare visits, reduces treatment burden, and reduces barriers to treatment adherence.

Rationale for Question Asked

Syphilis incidence among adolescents has increased globally by 21.7%, from 347.65 to 423.16 cases per 100,000 persons between 2010 and 2019.[3] The U.S. Preventive Services Task Force recommends screening nonpregnant adolescents and adults at increased risk for syphilis.[4] This rising incidence, along with global shortages of BPG and frequently reported penicillin allergies, highlights the need for effective alternative treatments for patients with penicillin allergy.[5-7] Treatment options are further limited during pregnancy, as penicillin remains the only recommended therapy.[8] This review evaluates ceftriaxone and doxycycline as alternative treatments for BPG.

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Characteristics of Included Studies by Outcome

Outcome 1: Serological Response[a]

Table 1. Serological Response CTX vs BPG

Author (year)	Study Type	Population	Benzathine Penicillin G (BPG)	Ceftriaxone (CTX)	Results	Notes
Liu et al. 2022	Systematic Review Meta-Analysis	*n* = 314 14 – 80 years Primary, secondary, tertiary, or latent syphilis	*n* = 153 2.4 MU, IM, weekly, 1-3 weeks	*n* = 161 1-2 g, IV, 1x/day 10-21 days	***Serological Response 12 months*** CTX compared to BPG: *RR* = 1.03, 95%CI (0.91, 1.17), *p* = .31; I^2 = 17%	*There were no statistical differences in serological response rates between ceftriaxone and BPG at the 12-month follow-up*

Table 2. Serological Response DOX vs BPG

Author (year)	Study Type	Population	Benzathine Penicillin G (BPG)	Doxycycline (DOX)	Results	Notes
Liu et al. 2022	Systematic Review Meta-Analysis	*n* = 516 14 – 80 years Primary, secondary, tertiary, or latent syphilis	*n* = 376 2.4 MU, IM, weekly, 1-3 weeks	*n* = 140 100 mg, PO, 2x/day 14-28 days	***Serological Response 12 months*** DOX compared to BPG: *RR* = 1.04, 95%CI (0.98, 1.10), *p* = .65, I^2 = 0%	*There were no statistical differences in serological response rates between doxycycline and BPG at the 12-month follow-up*

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		N = 82	*n = 41*	*n = 41*		*No statistically significant difference in the speed of achieving negative serologies between groups and subgroups of early syphilis and late syphilis at 12 months*
Zengarini et al. 2022	Cohort, prospective	*Mean age =40 primary, secondary, and early latent n = 17 latent syphilis n = 17*	*2.4 MU, IM, one dose*	*100 mg, PO, 2x/day, 14-28 days*	***Serological Response 12 months***[b] BPG 26/36 (72%) vs DOX 22/33 (67%O, p = 0.615	

[a]Zengarini et al. defined treatment success as RPR negativization or a ≥4-fold decline in RPR titer. This outcome is comparable to the serologic response used in the Liu et al. study, which was defined as either a VDRL/RPR negativization or a ≥4-fold decline in titer during follow-up.
[b]Fisher's exact test for statistical analysis

Summary and Certainty of Evidence for Serological Response

Serological Response Ceftriaxone vs BPG: 12 months. A meta-analysis of five included studies (two randomized controlled trials and three non-randomized controlled trials) from the systematic review (n = 314) measured the serological response to ceftriaxone versus BPG for the treatment of syphilis at 12-month follow-up.[1] Response rates for the 12-month serological response were available for only 314 (82%) of 383 participants, resulting in an RR = 1.03, 95%CI (0.91, 1.17); p = .31; I^2 = 17%, indicating no statistical difference between the use of ceftriaxone compared to BPG (see Table 1).

Serological Response Doxycycline vs BPG: 12 months. A meta-analysis of four included non-randomized studies from the systematic review (n = 376)[1] and one non-randomized cohort study (n = 82)[2] measured the serological response to doxycycline versus BPG for the treatment of syphilis at 12-months. For the 12-month serological response outcome, response rates were available for 376 (74%) of 511 participants from the systematic review, resulting in an RR = 1.04, 95% CI (0.98, 1.10), p = .65, I^2 = 0%. Response rates were available for 140 (74%) of 190 participants in the single non-randomized study, with results reported as percentages and Fisher's test for p-value (dox 22/33 (67%) vs BPG 26/36 (72%), p = .615). Findings from both studies demonstrate no statistically significant difference between the use of dox and BPG in the serological responses in the treatment of syphilis (see Table 2).

Certainty of Evidence for Serological Response.[9,10]

Ceftriaxone compared to BPG

For the single systematic review, the certainty of the evidence for serological response at 12 months was very low for ceftriaxone compared to BPG. The certainty of the evidence was downgraded for serious risk of bias and serious indirectness. The risk of bias was serious, as the evidence (randomized and non-randomized controlled trials) was combined, increasing concerns about confounding by shifting the weight toward the non-randomized studies. Indirectness was serious due to the application of adult literature to a pediatric population.

Doxycycline compared to BPG

For the single systematic review, the certainty of the evidence for serological response at 12 months was very low for doxycycline compared to BPG. The certainty of the evidence was downgraded for serious indirectness. Indirectness was serious due to the application of adult literature to a pediatric population. For the single non-randomized cohort study, the certainty of the evidence for serological response at 12 months is very low for doxycycline compared to BPG. The certainty was downgraded for serious indirectness. Indirectness was serious due to the application of adult literature to a pediatric population.

Search Methods

We searched EMBASE and PubMed from January 1, 2021, to July 3, 2026. This date range was chosen to capture literature published after the release of the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Infections Treatment Guidelines, 2021.[7]

Selection Criteria

Studies were eligible for inclusion if they were randomized controlled trials, observational studies, or systematic reviews in adolescents aged 12 – 18 years and/or adults 18 years and older with a diagnosis of primary, secondary, or early latent syphilis. We included studies that compared ceftriaxone or doxycycline to BPG for the serological response (resolution of infection). Studies were excluded if they included patients with other sexually transmitted diseases.

Identification of Studies

The search for suitable studies was completed on June 30, 2026, in EMBASE and PubMed. K. Berg, MD, A. Melanson, OTD, OTR/L, and A. Burns, PharmD, reviewed the 21 titles and/or abstracts found in the search and identified two systematic reviews and three cohort studies believed to answer the question. After an in-depth review of the studies, one systematic review and one cohort study answered the question(s).

Search Strategy and Results

See Appendices:

Appendix A: Search Strategy

Appendix B: Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11]

Table 2. Studies Not Included in this Review with Exclusion Rationale

Appendix C: Risk of Bias by Outcome

Findings from this review were presented to the question originator and the STI committee on September 3, 2026.

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Appendix A

Search Strategy

PubMed: January 1, 2021 – July 3, 2026
(Adolescent[MeSH] OR adolescen*[tiab] OR teen*[tiab]) AND (Syphilis[MeSH] OR syphilis[tiab]) AND (Ceftriaxone[MeSH] OR ceftriaxone[tiab]) AND (Penicillins[MeSH] OR "Penicillin G"[MeSH] OR penicillin*[tiab]) AND Humans[MeSH]

Embase: January 1, 2021 – July 3, 2026
('adolescent'/exp OR adolescen*:ti,ab OR teen*:ti,ab) AND ('syphilis'/exp OR syphilis:ti,ab) AND ('ceftriaxone'/exp OR ceftriaxone:ti,ab) AND ('penicillin'/exp OR 'penicillin g'/exp OR 'benzathine penicillin'/exp OR penicillin*:ti,ab) AND [humans]/lim AND [english]/lim

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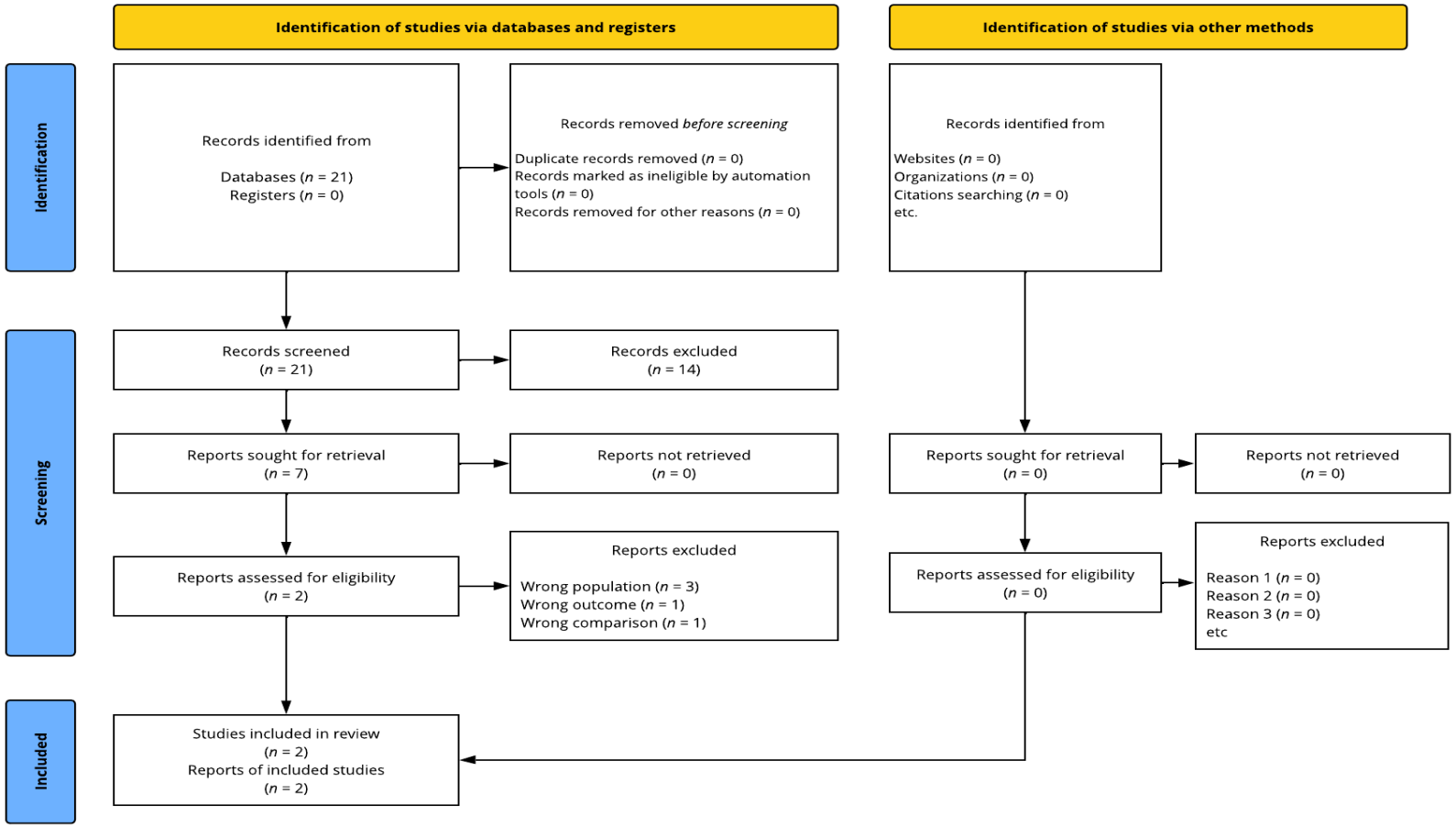
Appendix B

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11]



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Appendix C

Risk of Bias by Outcome: Serological Response

Using the A Measurement Tool to Assess systematic Reviews (AMSTAR 2), the single systematic review[1] was rated as low confidence and a high risk of bias.[13] One critical flaw was the failure to provide a list of excluded studies and justification for the exclusions (Item 7). Although the review met all other applicable critical domains, including protocol registration, risk-of-bias assessment, appropriate meta-analysis methods, consideration of risk of bias in interpretation, and assessment of publication bias, the presence of a single critical flaw resulted in a low confidence rating according to AMSTAR 2 guidance.

The single-cohort study scored 20 out of 24 on the Methodological Items for Non-randomized Studies (MINORS), indicating strong methodological quality. Strengths included a clear aim, consecutive enrollment, appropriate endpoints and follow-up, an accepted control, propensity score matching, and suitable analyses. Key limitations included a loss-to-follow-up rate of more than 9%, no prospective sample size or power calculation, a small sample size, and potential selection bias and residual confounding due to the retrospective design. These limitations reduce confidence in the precision of the findings despite the high MINORS score.