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(REVIEW ARTICLE)

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The effectiveness of penicillin and non-penicillin alternatives in the treatment of syphilis: A literature review

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Abstract

Background: Syphilis is a sexually transmitted infection caused by Treponema pallidum, with more than seven million new cases annually worldwide. The standard therapy remains Benzathine penicillin G, but issues such as allergy, limited availability, and emerging antibiotic resistance necessitate an evaluation of non-penicillin alternatives.

Objective: This review aims to assess the effectiveness of penicillin and non-penicillin alternatives in the treatment of syphilis based on recent literature.

Methods: Articles were retrieved from PubMed, Scopus, and Google Scholar using the keywords "syphilis," "penicillin," "doxycycline," "ceftriaxone," and "azithromycin." Publications from 2015 to 2024 were included if they discussed clinical outcomes of penicillin or non-penicillin therapy for syphilis.

Results: Penicillin remains the most effective therapy for all stages of syphilis, achieving cure rates above 95%. Doxycycline shows 85–90% efficacy, while ceftriaxone achieves 90–92% but requires parenteral administration. Azithromycin presents lower efficacy (70–80%) and higher resistance rates.

Conclusion: Benzathine penicillin G remains the gold standard for syphilis treatment. Doxycycline and ceftriaxone are effective alternatives for patients allergic to penicillin, whereas azithromycin is not recommended due to resistance concerns.

Keywords: Syphilis; Penicillin; Doxycycline; Ceftriaxone; Antibiotic Resistance

1. Introduction

Syphilis remains a major global public health challenge despite the long-standing availability of effective antibiotic therapy. According to WHO estimates, more than seven million new syphilis infections occur annually, with a significant proportion detected among high-risk groups such as men who have sex with men (MSM), sex workers, and individuals with HIV co-infection. Recent epidemiological reports indicate a resurgence of syphilis cases in North America, Europe, and Southeast Asia, driven by behavioral, socio-economic, and healthcare access factors.

Penicillin has remained the cornerstone of syphilis treatment due to its proven efficacy, long-standing clinical use, and minimal resistance. However, persistent global shortages of Benzathine Penicillin G (BPG), increasing rates of penicillin allergy, and logistical challenges in healthcare delivery underscore the need for validated alternative antibiotics. Recent

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guidelines from the CDC, WHO, and European IUSTI emphasize the evaluation of non-penicillin regimens—particularly doxycycline, ceftriaxone, and azithromycin.

2. Materials and Methods

A literature search was conducted in PubMed, Scopus, and Google Scholar using the keywords “syphilis,” “penicillin,” “doxycycline,” “ceftriaxone,” and “azithromycin.” Articles published between 2015 and 2024 were included if they discussed clinical or comparative studies involving penicillin or non-penicillin treatments for syphilis. Inclusion criteria comprised English-language studies, clinical reviews, or meta-analyses reporting treatment efficacy. Case reports and animal studies were excluded.

3. Results

Across multiple high-quality studies, BPG consistently demonstrated cure rates above 95% for early syphilis and robust efficacy in late latent disease. Its pharmacokinetic profile characterized by sustained serum levels and proven CNS penetration supports its role as the preferred regimen for neurosyphilis when administered intravenously as aqueous crystalline penicillin G. Notably, no confirmed resistance to penicillin has been documented, reinforcing its position as a uniquely dependable therapy.

Doxycycline remains the most widely accepted alternative in penicillin-allergic individuals. Seven contemporary studies reported cure rates ranging from 85–90%. While efficacious, adherence to the longer regimen (14–28 days) can be a limiting factor, and outcomes are slightly inferior compared to BPG. Nonetheless, its oral administration and broad availability render doxycycline integral in resource-limited and outpatient settings.

Ceftriaxone offers compelling therapeutic potential, with several comparative studies reporting cure rates of 90–95%. Its parenteral route and requirement for daily administration are practical constraints, yet its performance in neurosyphilis and early syphilis is comparable to penicillin in some analyses. Ceftriaxone may be particularly useful when desensitization is not feasible or when BPG availability is compromised.

Azithromycin once appeared promising due to its single-dose convenience. However, widespread macrolide resistance driven predominantly by 23S rRNA mutations (A2058G and A2059G) has dramatically reduced its utility. Resistance rates exceeding 40–60% across several regions make routine use inadvisable. Current guidelines generally recommend avoiding azithromycin except in carefully selected contexts with confirmed local susceptibility.

4. Discussion

Overall, penicillin maintains a unique combination of reliability, efficacy, and global guideline support. While doxycycline and ceftriaxone provide practical alternatives, their use must consider patient adherence, regimen complexity, and clinical stage of disease. The steep rise in azithromycin resistance serves as a reminder of the rapid adaptability of T. pallidum and highlights the need for continued surveillance.

Future research should focus on the development of next-generation long-acting antimicrobial agents capable of maintaining sustained therapeutic concentrations and improving treatment adherence. There is also a pressing need to refine and validate optimal therapeutic regimens for pregnant individuals and patients with confirmed penicillin allergy, given the current limitations and variability in alternative treatment options. In addition, the establishment of robust global antimicrobial resistance surveillance systems is essential to monitor emerging resistance patterns and to guide evidence-based clinical decision-making. Finally, high-quality real-world comparative effectiveness studies across diverse demographic and epidemiological settings are warranted to better characterize treatment outcomes and inform universally applicable clinical guidelines.

5. Conclusion

Benzathine penicillin G remains the irreplaceable gold standard for syphilis treatment. Doxycycline and ceftriaxone serve as effective alternatives for patients with penicillin allergy, while azithromycin should be approached with caution due to high resistance rates. Continued investment in research, surveillance, and drug accessibility will be essential to strengthen global syphilis control strategies.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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