Letters

Neurosyphilis: A diagnostic conundrum with many faces

We have read with great pleasure the article by Campbell et al entitled 'Syphilis the great mimic: Forgotten but not gone'.[1] Syphilis is on the rise in many countries. We would like to highlight some noteworthy aspects of neurosyphilis.

Skin and mucous membrane lesions, lymphadenopathy and the patient's lifestyle might facilitate the diagnosis, but asymptomatic disease, a sense of shame, insufficient attention to health, late disease-associated cognitive impairment and personality changes can all impede collecting these data. In late neurosyphilis, Argyll–Robertson pupils are not always present. Inconsistent use of barrier contraception is a recognised risk factor for syphilis. Nonetheless, contact with any uncovered infected epithelium without a barrier device might result in contracting the disease. Neurosyphilis cannot be ruled out in patients with no previous history of high-risk sexual behaviour, as non-sexual transmission of *Treponema pallidum* has been reported, in particular in households shared with an infected person.[2] Occasionally, patients with the disease deteriorate over a short period of time. Neurosyphilis constitutes 5.4% of cases of rapidly progressive dementia, with other etiological causes (which can be included in the differential diagnosis) including metabolic diseases (16.8%), Creutzfeldt–Jakob disease (13.4%), Alzheimer's disease (11.4%), carbon monoxide poisoning (8.1%), and dementia with Lewy bodies (5.4%).[3]

Benzathine penicillin G (BPG) and doxycycline are approved by the World Health Organization (WHO) for both early and late syphilis; intramuscular BPG remains the gold standard.[4] Oral antibiotics amoxicillin and linezolid are under trial (NCT06921213, NCT06877351, NCT05069974). In neurosyphilis, BPG is the drug of choice, given a strong bactericidal effect and safety profile. In cases of allergy to penicillin, desensitisation should be performed; ceftriaxone is also used (given low cross-reactivity with penicillin, it is contraindicated in patients with previous penicillin anaphylaxis).[5] If desensitisation is impossible, the WHO guidelines permit the prescription of doxycycline, except for pregnant patients, for whom erythromycin is indicated.[4] Nonetheless, in neurosyphilis, the use of antibiotic alternatives to penicillin requires more research.[5]

In conclusion, neurosyphilis is a diagnostic conundrum characterised by the heterogeneity of symptoms and a large spectrum of differential diagnoses; early therapy initiation is crucial to preventing disease progression.

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References

1. Campbell DE, Uribe E, Mothobi N, Huffam S, Muleme M, Athan E. Syphilis the great mimic: Forgotten but not gone. Aust J Gen Pract 2024;53(10):714–18. doi: 10.31128/AJGP-06-23-6858.
2. Moscatelli G, Moroni S, García Bournissen F, et al. Acquired syphilis by nonsexual contact in childhood. Pediatr Infect Dis J 2021;40(10):892–98. doi: 10.1097/INF.0000000000003215.
3. Liu X, Sun Y, Zhang X, et al. Prevalence and outcomes of rapidly progressive dementia: A retrospective cohort study in a neurologic unit in China. BMC Geriatr 2023;23(1):142. doi: 10.1186/s12877-023-03841-1.
4. WHO Guidelines for the Treatment of Treponema pallidum (Syphilis). World Health Organization, 2016. Available at www.who.int/publications/i/item/9789241549714 [Accessed 30 May 2025].
5. Callado GY, Pardo I, Gutfreund MC, et al. Insights into treatment alternatives for neurosyphilis: Systematic literature review and meta-analysis. Sex Transm Dis 2024;51(10):641–47. doi: 10.1097/OLQ.0000000000001983.

Response to Letter to the Editor regarding article: Syphilis the great mimic: Forgotten but not gone

I would like to thank the authors for their letter in response to the article 'Syphilis the great mimic: Forgotten but not gone', published in the Journal's October 2024 issue on infectious diseases.[1]

This letter extends from our manuscript to further emphasise the importance of considering syphilis and, indeed, neurosyphilis in all people regardless of age or sexual history. As discussed in our manuscript, neurosyphilis may be subclinical or present subtly with a wide spectrum of non-specific symptoms at any stage of disease.

Although a detailed discussion of emerging treatments for neurosyphilis was not within the scope of our article, I would like to

highlight that there is considerable variation between European,[2] UK,[3] US[4] and Australian[5] guidelines for the management of neurosyphilis. At the time of publication, intravenous benzylpenicillin remains the only regimen recommended in the Australian guidelines for treatment of neurosyphilis.[5] I thank the authors for highlighting intramuscular benzathine penicillin G, which is the mainstay of treatment in the UK,[2] as well as non-penicillin alternatives currently undergoing clinical trials. I eagerly await these results in the hope that we may find acceptable oral alternatives that allow for safe and effective treatment of neurosyphilis without the need for hospital admission.

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References

1. Campbell DE, Uribe E, Mothobi N, Huffam S, Muleme M, Athan E. Syphilis the great mimic: Forgotten but not gone. Aust J Gen Pract 2024;53(10):714–18. doi: 10.31128/AJGP-06-23-6858.
2. Janier M, Unemo M, Dupin N, Tiplica GS, Potočnik M, Patel R. 2020 European guideline on the management of syphilis. J Eur Acad Dermatol Venereol 2021;35(3):574–88. doi: 10.1111/jdv.16946.
3. Kingston M, French P, Higgins S, et al; Members of the Syphilis guidelines revision group 2015. UK national guidelines on the management of syphilis 2015. Int J STD AIDS 2016;27(6):421–46. doi: 10.1177/0956462415624059.
4. Syphilis. In: Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report. Sexually Transmitted Infections Treatment Guidelines, 2021. Atlanta, GA.
5. Syphilis. In: Therapeutic Guidelines. Therapeutic Guidelines Limited, 2025. Available at www.tg.org.au [Accessed 6 July 2025].

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