The patient continued to have episodes of fever, which had been occurring since admission. On day 14, the patient developed leucocytosis and blood cultures were drawn, which grew MRSA. The MIC of vancomycin increased to 2 mg/L, with that of daptomycin remaining at 0.38 mg/L.

Since the patient continued to be symptomatic, irrigation and debridement was scheduled, but due to surgeon availability issues this was not performed until hospital day 19. A sample was obtained during the procedure and cultured, and on day 22, after >2 weeks of treatment with daptomycin, MRSA grew with a daptomycin MIC of 3 mg/L (daptomycin-non-susceptible S. aureus (DNSSA)). The primary cause of the daptomycin failure was most likely a delay in incision and drainage of the abscesses. Experimental osteomyelitis models have shown selective resistance with daptomycin monotherapy, which possibly contributed to the resistance in this case. Daptomycin was discontinued and, unfortunately, vancomycin was restarted over the weekend.

After the patient became bacteraemic on day 14, we recommended a TEE, which was ordered but not performed until day 23. Lesions were found on the left coronary cusp (LCC) and the tricuspid valve, consistent with endocarditis. Vancomycin was discontinued, since current expert opinion states alternative antimicrobials should be considered when the vancomycin MIC is ≥2 mg/L, due to treatment failures. Considering this and the severity of infection in this patient, we turned to salvage therapy options and ceftaroline (600 mg intravenously every 12 h), which had an Etest MIC of 0.5 mg/L, was chosen.

Ceftaroline is a fifth-generation cephalosporin with activity against MRSA. Ceftaroline was chosen for a number of reasons. First, it is rapidly bactericidal. Ho et al. reported sterilization in 13 days in a case of endocarditis. Also, the incidence of thrombocytopenia with long-term use is low, which was particularly important since our patient had a history of thrombocytopenia secondary to hepatitis. Finally, a literature search revealed a series of case reports showing successful use of ceftaroline in the treatment of MRSA endocarditis and an experimental model demonstrating potential use in osteomyelitis.

Subsequent blood cultures drawn on days 29 and 32 were negative. On day 32, a repeat irrigation and debridement was performed. After 37 consecutive days of ceftaroline treatment, a TEE showed resolution of echodensities at the base of the tricuspid valve and a stable, fibronodular lesion on the LCC. Ceftaroline was continued for a total of 44 days, with no further episodes of bacteraemia, leucocytosis or fever, which completed his treatment. The patient was discharged home but was lost to follow-up.

This case report demonstrates the importance of surgery for the primary treatment of abscesses and osteomyelitis. A delay in surgical intervention was likely the cause of endocarditis and the development of daptomycin resistance in this patient. Elevated vancomycin MICs have been associated with increased daptomycin MICs, suggesting the possibility of cross-resistance, which might also have been seen in this case. Combined with proper surgical treatment, the efficacy and tolerability of ceftaroline for the treatment of concomitant methicillin-resistant and DNSSA endocarditis and osteomyelitis was demonstrated in this case.

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This study was carried out as part of our routine work.

**Transparency declarations**

None to declare.

**References**


Sir,

Over time Neisseria gonorrhoeae has developed resistance to a wide range of antimicrobials, including cephalosporins, limiting treatment options.1 We report a case of persistent pharyngeal N. gonorrhoeae despite administration of 500 mg of ceftriaxone by intramuscular injection, a dose exceeding that currently recommended in some countries for gonorrhoea. We obtained informed consent from the index patient to publish this report.

A homosexual man presented to a Melbourne clinic in 2010 (day 0) complaining of anal discomfort. His regular male partner had been diagnosed with gonorrhoea and therefore he was given 500 mg of ceftriaxone by intramuscular injection. Both rectal and pharyngeal swabs grew N. gonorrhoeae. On day 22, a repeat pharyngeal swab grew N. gonorrhoeae. He returned on day 34. A third pharyngeal swab was taken before he was given 2 g of azithromycin. N. gonorrhoeae was again isolated. He reported that he had not had any sexual contact since his first visit.

Pharyngeal and rectal swabs taken on day 41 were negative for N. gonorrhoeae on culture and by Abbott m2000 real-time PCR testing.

The patient’s regular male partner presented to a general practitioner with conjunctival and urethral gonorrhoea confirmed by nucleic acid amplification testing (NAAT) and was treated with cefalexin, doxycycline and amoxicillin. Pharyngeal and rectal swabs for culture and urine NAAT for N. gonorrhoeae taken 2 months later were negative. He reported that the last time he had sex was with his regular partner and that this was prior to day 0 above.

Isolates were identified as N. gonorrhoeae based on Gram’s stain, oxidase, carbohydrate utilization reactions and the MicroTrak® N. gonorrhoeae Culture Confirmation Test (Trinity Biotech) and confirmed by porA pseudogene and opa gene PCR assays.

MICs were determined by agar plate dilution using the method of the Australian Gonococcal Surveillance Programme (AGSP)2 and Etests (AB bioMérieux). For all four isolates and all antimicrobials, the MIC values fell within one dilution of each other. The MIC values obtained and the AGSP interpretive categories were as follows: ceftriaxone, 0.03–0.06 mg/L (decreased susceptibility); ciprofloxacin, 8–16 mg/L (resistant); penicillin, 1–2 mg/L (less susceptible); spectinomycin, ≤64 mg/L (susceptible); and azithromycin, 0.25–0.5 mg/L (susceptible).

The rectal and pharyngeal isolates from day 0 and the pharyngeal isolates from days 22 and 34 were examined by PFGE. Indistinguishable PFGE patterns were obtained for all four isolates.

N. gonorrhoeae multi-antigen sequence typing (NG-MAST) of isolates from day 0 and day 22 identified them as sequence type (ST) 1407. The isolate from day 34 was ST4950. ST4950 contains a 3 base duplication in the porA allele compared with ST1407, most likely due to a DNA replication error of the original ST1407 isolate in situ. Partial sequencing of the penA and porB genes revealed that all four isolates contained a mosaic penicillin-binding protein 2 type XXXIV and porB1b alterations G101K/A102N.

N. gonorrhoeae was isolated from pharyngeal cultures taken 22 and 34 days after 500 mg of ceftriaxone. The day 22 isolate was indistinguishable from the day 0 isolate when compared by PFGE and NG-MAST. The day 34 isolate was also indistinguishable by PFGE, but was of a different, yet closely related, NG-MAST type. These findings, together with the reported absence of sexual activity, suggests the failure of 500 mg of ceftriaxone to eradicate pharyngeal N. gonorrhoeae. While re-infection could explain the results, the index patient and partner reported sexual abstinence following treatment.

All four isolates showed decreased susceptibility to ceftriaxone with an MIC value of 0.03–0.06 mg/L. According to the AGSP the ceftriaxone MIC range 0.06–0.125 mg/L corresponds to decreased susceptibility and this is the highest MIC category reported for ceftriaxone. In 2010, in Australia, 4.8% of isolates tested had an MIC of ceftriaxone in this range.3 Higher ceftriaxone MIC values (0.125–0.25 mg/L) have been reported elsewhere,4 but not in Australia. These higher MIC values could in part be attributed to the use of EUCAST criteria elsewhere, based on a different MIC methodology. The isolates were NG-MAST type ST1407 (or the closely related ST4950), which is a clone of N. gonorrhoeae with decreased susceptibility to extended-spectrum cephalosporins that has disseminated globally5 and was associated with genital gonorrhoea treatment failure using 400 mg of cefixime.6 The isolates also harboured a mosaic penicillin-binding protein 2 type XXXIV and porB1b alterations G101K/A102N, recognized contributors to cephalosporin resistance.7

While the high ceftriaxone MICs for the above isolates would have contributed to pharyngeal treatment failure for the index patient, it should be noted that isolates with such MICs are increasingly being found in pharyngeal samples, but with only one other report of treatment failure at the 500 mg dose reported from Sweden.8–10 This case may represent a threshold of antimicrobial activity based on dose, site and isolate MIC.11 While treatment failure may be possible, it may not necessarily occur readily under these conditions. Nevertheless, with rising ceftriaxone MICs12 further treatment failures, both genital and extragenital, would seem inevitable.

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Are artemisinin-based combination therapies effective against Plasmodium malariae?

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Sir,

Plasmodium malariae is the least studied of malaria parasites, probably because of its low prevalence and milder disease. It is rather common in Africa and in the south-west Pacific and is frequently found in the setting of mixed infections, but it is relatively rare in imported malaria. The standard treatment for P. malariae malaria is chloroquine, but very little is known about its susceptibility to antimalarials, such as artemisinin-based combination therapies (ACTs), which are first-line treatment for Plasmodium falciparum malaria. In two studies, artemunate alone and artesunate/lumefantrine proved effective against P. malariae in Gabon,1,2 but two cases of P. malariae infection after chemoprophylaxis (mefloquine and atovaquone/proguanil) were reported in France.3

The issue of introducing a unified ACT-based treatment policy for all plasmodia, in order to simplify the treatment of malaria, is currently being discussed.

A 44-year-old male of African origin, resident in Italy for 10 years, was admitted to our hospital in October 2009, after 6 days of fever and headache. He had returned from Uganda 14 days earlier and had not taken malaria chemoprophylaxis. He had been HIV positive since 1999 and was on treatment with efavirenz/emtricitabine/tenofovir disoproxil (viral load suppressed, CD4+ count: 400 cells/mm3). He was a type 2 diabetic, being only on diet control.

P. falciparum malaria was diagnosed (parasitaemia: 7500 trophozoites/mm3, 0.13%) and the patient was treated with 20/120 mg of artesunate/lumefantrine (Riamet®, Novartis Pharma Schweiz-AG, Bern), four tablets twice daily for 3 days, under supervision. The fever resolved within 48 h; his thick blood film became negative for plasmodia within 72 h and was confirmed negative on day 30.

After 8 days he started to complain about fever with a 3 day periodicity. The patient was readmitted to our hospital and a thin blood film showed P. malariae schizonts. Chloroquine treatment at the standard dose (1.5 g over 3 days) was started immediately: rare trophozoites of P. malariae were still present on day 3, but his smear was negative on days 7 and 40.

The patient had not left Italy after his previous episode of malaria.

The combination artesunate/lumefantrine is recommended for the treatment of acute uncomplicated P. falciparum malaria, but no data are provided by the manufacturers about its effectiveness against P. malariae.

The activity of artesunate is mediated by free radicals damaging the membranes of young and mature trophozoites and gametocytes; lumefantrine inhibits the haem polymerase activity of the parasite and kills mature trophozoites. Both drugs do not have an effect on the pre-erythrocytic stages.

Three possible explanations for the ineffectiveness of artesunate/lumefantrine are considered.

First, the plasma levels of the drugs could be insufficient, due to poor absorption or to interaction between lumefantrine and efavirenz, both of which are substrates of cytochrome CYP450-