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First linezolid- and vancomycin-resistant *Enterococcus faecium* strain in Taiwan

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Sir,

Linezolid is an important therapeutic option for treatment of infections caused by resistant Gram-positive bacteria.[1] Although this agent has only been used in clinical practice for a relatively short period of time, there have already been several reports of linezolid resistance in *Staphylococcus aureus* and vancomycin-resistant enterococci (VRE).[1,2] To our knowledge, this is the first report of a linezolid-resistant *Enterococcus faecium* strain isolated in Taiwan.

The 51-year-old woman developed disseminated *Mycobacterium fortuitum* infection and presented with fever, lymphadenopathy and bacteraemia in December 1999. During the 9 months of treatment course in hospital and in outpatient clinic, she received amikacin, ciprofloxacin, doxycycline, clarithromycin, or rifabutin. Splenic abscess, granulomatous hepatitis, and generalized lymphadenopathy developed in September 2000. Culture of liver biopsy and bone marrow both yielded *Mycobacterium avium* complex (MAC). She was treated with clarithromycin, ciprofloxacin and rifampicin for 6 months followed by ciprofloxacin and clarithromycin for 1 year.

In December 2002, the patient was admitted due to fever and abdominal pain for 2 weeks. Abdominal sonography showed multiple lymph nodes over the mesenteric and aortic areas. Blood cultures and bone marrow cultures carried out during the admission all yielded MAC. During the following 20 months of hospitalization, progressive osteomyelitis developed over the cervical and thoracic spine complicated with retropharyngeal and prevertebral abscess, quadriparesis, diffuse lymphadenopathy, granulomatous hepatitis with hepatic calcification, and empyema thoracis due to MAC. Several episodes of nosocomial pneumonia also occurred and necessitated ventilator support. Her condition was refractory to long-term treatment with many antimycobacterial agents, including ciprofloxacin (1000 mg every day, 1030 days), clarithromycin (1000 mg every day, 1020 days), azithromycin (500 mg every day, 188 days), imipenem (2 g every day 170 days), amikacin (500 mg, every two days, 145 days), clofazimine (100 mg every day, 175 days), mefloquine (500 mg thrice weekly, 149 days), linezolid (600 mg every 12 h, 155 days), and interferon-γ (75 μg thrice weekly) for 2 months (Figure 1).

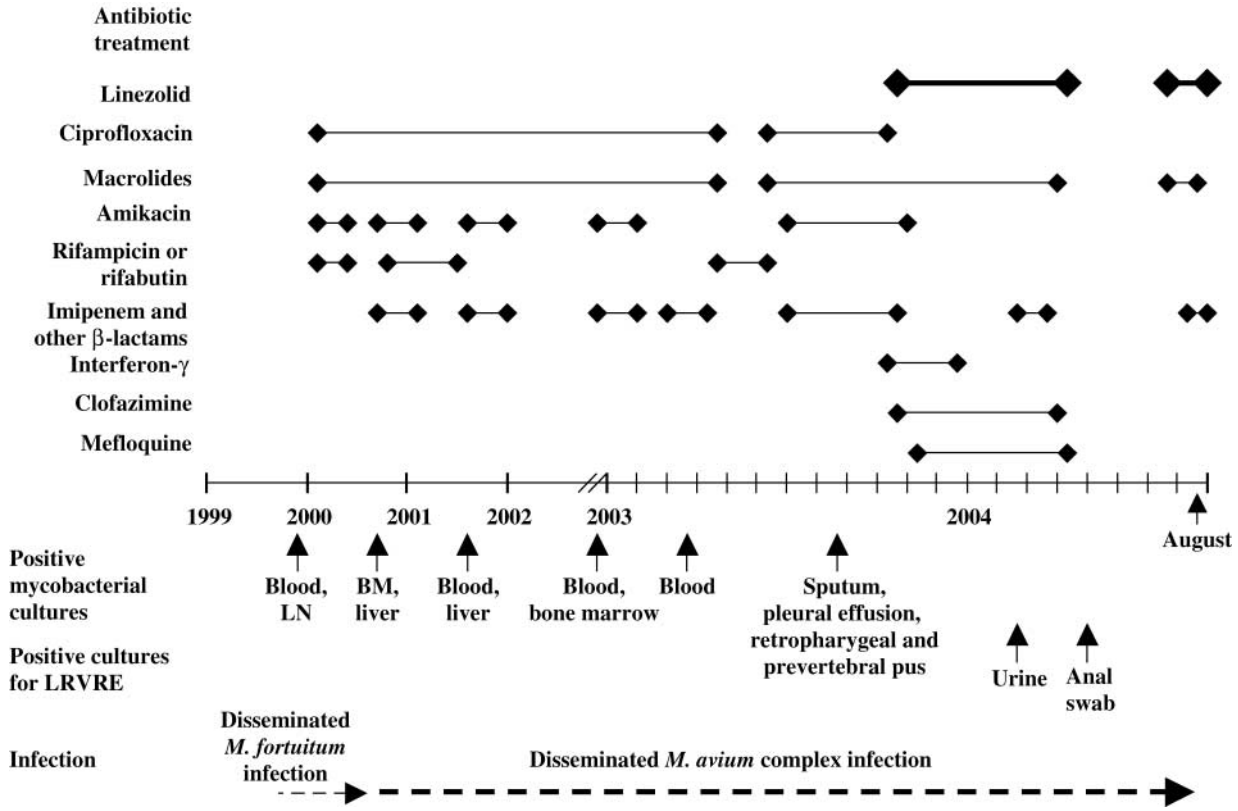

Figure 1. Timeline of clinical course of a patient with disseminated mycobacterial infection. LRVRE, linezolid- and vancomycin-resistant enterococci.

A urine specimen on 1 March 2004 (isolate A) and an anal swab (isolate B) on 13 April 2004 both yielded isolates of vancomycin-resistant *E. faecium* (VRE). There was no evidence of urinary tract infection or anal lesion due to VRE. The patient had received linezolid treatment for 122 days when linezolid-resistant VRE (isolate A) was recovered.

MICs for the two isolates were determined using the agar dilution method for all agents, except daptomycin, for which MICs were determined by the broth microdilution method (TREK Diagnostic Systems, Cleveland, OH, USA). The two isolates (isolates A and B) exhibited identical MICs for the following agents: penicillin, ≥128 mg/L; vancomycin, ≥128 mg/L; teicoplanin, ≥128 mg/L; telithromycin, 8 mg/L, quinupristin–dalfopristin, 2 mg/L; daptomycin, 4 mg/L; tigecycline, 0.03 mg/L; and linezolid, 32 mg/L. These two VRE isolates had VanA phenotype and were susceptible to quinupristin–dalfopristin. Sequencing analysis of PCR amplicon of central loop of domain V of the 23S rRNA by two primers corresponding to 2049 to 2767 bp of the two isolates was carried out as previously described.[3] A mutation (U2357A) in the domain V of the 23S rRNA gene was found in the two isolates. PCR-restriction fragment length polymorphism analysis of the ribosomal DNA amplicons with *Nhe* I failed to detect the G2576T mutations.[4] Pulsed-field gel electrophoresis analysis of the two isolates showed the same *Sma* I patterns.

This is the first report of isolation of a linezolid-resistant *E. faecium* strain in Taiwan. In our patient, the emergence of resistance to linezolid was associated with the prolonged use of linezolid in regimens for the treatment of MAC infection. Linezolid is not indicated for treatment of MAC infection due to poor *in vitro* activity against MAC isolates,[5] although successful treatment of refractory disseminated *M. avium* complex infection with the addition of linezolid and mefloquine has been reported.[6] The great majority of linezolid- and vancomycin-resistant *E. faecium* infections reported have occurred in patients treated with linezolid, although nosocomial spread had also occurred.[3] At our hospital, linezolid was introduced into clinical use in 2002 and a five-fold increase in consumption was noted in 2003 (1.16 DDD per 1000 patient-days) compared with that in 2002 (0.225 DDD per 1000 patient-days).

In vitro investigations and clinical studies have implicated a G2576U mutation in the rRNA of linezolid-resistant *Enterococcus faecalis*, *E. faecium* and *S. aureus*.[1–3] Interestingly, two isolates from our patient were found to have a new mutation at U2357A not previously reported in linezolid-resistant enterococci. Further studies should be conducted to elucidate the potential significance of the mutation for resistance to linezolid. The U2357A mutation has been described previously in a linezolid-resistant *Streptococcus oralis* by Mutnick *et al.*[7] This resistant isolate emerged while on linezolid therapy and had a G2576U mutation with additional changes at U2132A, U2211G and U2357A. However, these authors also failed to demonstrate that the mutation had any causal effect on linezolid resistance.

In summary, we report a linezolid- and vancomycin-resistant *E. faecium* strain isolated from a patient with disseminated MAC infection after long-term linezolid therapy. This sentinel isolate underscores the importance of using linezolid with caution and indicates the need for routine testing of all VRE isolates for linezolid susceptibility.

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Severe myopathy and possible hepatotoxicity related to daptomycin

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Sir,

A 52-year-old male with a history of intravenous drug abuse, idiopathic thrombocytopenia, hyperlipidaemia and hepatitis C was admitted to hospital with low back pain, fevers and chills. MRI findings were compatible with L3–L4 discitis and osteomyelitis. The patient underwent an open biopsy where Gram-positive cocci were observed on Gram stain, but cultures were negative. The patient was started on vancomycin, but this was discontinued and daptomycin was initiated after the patient developed a generalized erythematous rash with facial angiooe-