isolate 4 as donor, transconjugants were selected on MacConkey agar with 2 mg/L cefotaxime and 50 mg/L nalidixic acid. Both types of blaCTX-M-14-carrying plasmids proved to be conjugative (Figure 1a) and harboured the blaCTX-M-14 gene on an EcoRI-fragment of ~18 kb. All three S. Enteritidis isolates showed closely related XbaI-PFGE-patterns, determined as previously described.2 The only difference in the fragment patterns was an extra band of ~75 kb in the cefotaxime-resistant isolates 2 and 3 (Figure 1b), which hybridized with the CTX-M-14 probe (data not shown).

Based on these observations, it was assumed that the child was infected with a strain which developed an ESBL phenotype during the treatment. Because data were not available about intestinal flora of the patient before the bacteraemic episode, we cannot exclude the possibility that the child acquired an invasive cefotaxime-susceptible and a cefotaxime-resistant S. Enteritidis as well as an ESBL-producing E. coli at the same time before hospital admission. Simultaneous transmission of ESBL-producing E. coli with susceptible Salmonella enterica from a common source has been previously reported1 in a Salmonella outbreak in a summer camp. None of the samples from campers or food-handlers yielded resistant salmonellae and, in contrast with our case, no person received antibiotic therapy.

The family of the CTX-M-type ESBLs comprises 40 enzymes, subclassified into five major groups by their similar amino acid sequences: CTX-M-1, M-2, M-8, M-9 and M-25 groups.4 Salmonella isolates have been found to express CTX-M-2, M-3, M-4 and M-9 enzymes in serotypes Typhimurium and Enteritidis isolated in South America and Europe.4 Until now, CTX-M-14 has been described in several enterobacterial species, but not in Salmonella isolates.5 In Spain, the only report of a CTX-M-type production in Salmonella was that described by Simarro et al.1 in 1997. In this study, four Salmonella enterica Vichirot strain were reported with CTX-M-9 production in Barcelona and Murcia. Furthermore, CTX-M-14 β-lactamase has previously been found in the north-west area of Spain6 in different E. coli strains, causing infections in 17 patients. Our findings provide the first evidence of CTX-M-14 β-lactamase in Salmonella enterica serotype Enteritidis. The observation that the blaCTX-M-14 gene is located on a conjugative plasmid which can transfer in vivo between E. coli and Salmonella Enteritidis strongly suggests that such transfer events can also occur in vivo.

Acknowledgements
We thank the personnel of the NRL-Salm (BfR, Berlin), especially E. Junker and M. Jaber, for their helpful assistance. This study was supported by REIPI grant; CO3/14, Spain.

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Journal of Antimicrobial Chemotherapy
DOI: 10.1093/jac/dkh199
Advance Access publication 29 April 2004

Severe bilateral optic neuritis associated with prolonged linezolid therapy
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Keywords: prolonged therapy, foreign body infections, methicillin-resistant Staphylococcus epidermidis

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Sir,

Linezolid is the first member of the oxazolidinones with excellent in vitro activity against Gram-positive bacteria including methicillin-resistant staphylococci.1 Several reports describe its possible use for the treatment of prosthetic joint infections caused by these strains.1–3 In these cases, prolonged antibiotic therapy is necessary but may increase the risk of long-term drug-related adverse events. Linezolid is usually well tolerated and few adverse effects are described.1,4 However, its safety during prolonged use (>28 days) has not been systematically evaluated in controlled clinical studies.5 We describe a case of severe, acute and partly irreversible bilateral optic neuritis occurring after 41 weeks of therapy with linezolid indicated for a persisting methicillin-resistant Staphylococcus epidermidis (MRSE) prosthetic knee infection.

A 72-year-old woman with a history of rheumatoid arthritis and type 2 diabetes mellitus underwent total arthroplasty of both knees in 1995. In June 1997, she presented with a left prosthetic joint infection and bacteraemia due to MRSE. A two-stage surgical procedure was performed, with re-implantation performed after a 14 week course of rifampicin plus ofloxacin. In 1999, she experienced transient fever, joint pain and loosening signs on plain X-rays. Debridement and aspiration of the joint were performed and the cultures yielded MRSE. Antibiotherapy was not initiated by surgeons. A few weeks later, persisting cutaneous sinus drainage appeared. At that time, the patient refused further surgery. Oral therapy with high dosage trimethoprim–sulfamethoxazole (15 and 75 mg/kg/day, respectively) was started. Because of gastrointestinal intolerance and transient hyperkalaemia, the dosage was progressively reduced to a ‘suppressive lifelong’ therapy (160 mg/800 mg twice a day). How-

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ever, in November 2000, the patient experienced pain and sinus drainage. The implant was then removed and an arthrodesis performed after 5 weeks of teicoplanin therapy (loading dose: 12 mg/kg/day for 3 days, then 6 mg/kg/day; trough level between 11 and 16 µg/dL). Despite ongoing therapy with teicoplanin (6 mg/kg/day), a new sepsis occurred 2 weeks later: several blood cultures and tissue cultures of the thigh yielded both MRSE and *Escherichia coli*, suggesting not only the persistence of infection with MRSE but also the occurrence of a deep nosocomial infection of that site with *E. coli*. *S. epidermidis* cultures of the blood was susceptible to linezolid (MIC = 0.5 mg/L), rifampicin and vancomycin but intermediate to teicoplanin (MIC = 16 mg/L) and resistant to trimethoprim–sulfamethoxazole, clindamycin and fluoroquinolones. For technical reasons, an antibiogram of the MRSE isolated from tissue cultures was not performed, but *E. coli* was susceptible to all antibiotics tested both in blood and tissue samples.

Therapy with linezolid plus rifampicin (for MRSE) and ciprofloxacin (for *E. coli*) was initiated. Linezolid was obtained through Pharmacia & Upjohn’s compassionate-use protocol and was well tolerated based on the weekly laboratory testings. The patient was progressively able to walk with two canes. It was planned to remove the material after consolidation and to continue antibiotics for 3 months after this, with a maximum of 12 months of antibiotic therapy. Forty-one weeks later the patient presented to her ophthalmologist with sudden blurred vision. The situation worsened rapidly and 3 weeks later antibiotics were stopped and the patient was hospitalized.

At that time, concomitant medications were insulin, citalopram and lorazepam. Repeated funduscopic examinations (excepted for ocular hypertension), computed tomography scan and magnetic resonance imaging of the brain, lumbar puncture and dosage of vitamin B1 and B6 were normal. Visually evoked potential testing (VEP) confirmed severe bilateral optic neuritis. Therapy with methylprednisolone (1 g/day, 5 days) was started. The visual acuity recovered but not completely, whereas ocular hypertension normalized rapidly. Eight months later, VEP showed mild abnormalities predominantly in the left eye.

Optic neuritis has been associated with the use of antimycobacterial agents such as isoniazid and ethambutol, but not with rifampicin or with fluoroquinolones. Only neurotoxicity—essentially central nervous system toxicity—has been reported with the use of fluoroquinolones, including ciprofloxacin, in 0.9%–7.4% of patients. In our patient, we believe that linezolid was the most probable offending agent since all other causes were reasonably excluded, e.g. glaucoma, multiple sclerosis and toxic optic neuropathies. In a recent compassionate-use programme of linezolid, peripheral neuropathy was reported in three cases, all of which involved long durations of therapy (mean, 95 days). In these three cases, it is possible that several underlying diseases and drugs contributed partially to this side effect. In our case, linezolid is the most likely cause, but it is possible that the combination with rifampicin, and/or ciprofloxacin has enhanced the toxicity.

In conclusion, we suggest that peripheral or optic neuropathy could be a rare but potentially severe complication linked to prolonged linezolid therapy.

References


