Management of quinolone-resistant typhoid osteomyelitis

Introduction

Multi-drug resistance is already prevalent in *Salmonella enterica*; as the incidence of isolates with decreased susceptibility to ciprofloxacin increases, treatment options for enteric fever and complications such as osteomyelitis become limited. This article presents two patients with quinolone-resistant enteric fever with bone involvement and describes successful outcomes using oral azithromycin.

Discussion

These cases illustrate an uncommon but important complication of enteric fever. First noticed by Paget more than 100 years ago (Paget, 1876), bone involvement is estimated to occur in less than 1% of infections (Murphy, 1916) but it necessitates prolonged and often complex treatment (Santos and Sapico, 1998).

The emergence of resistance in salmonellae has compromised the usefulness of many antimicrobial agents. Multidrug resistance in salmonellae is defined as resistance to ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole, which are traditionally first-line agents for the treatment of enteric fever. The multidrug resistance phenotype has become common in *S. typhi* and, to a lesser extent, *S. paratyphi* (Parry and Threlfall, 2008) and this has led to greater reliance on other agents, particularly fluoroquinolones.

Promising results with ciprofloxacin suggested that it was more effective in the treatment of uncomplicated enteric fever in areas with high rates of multidrug resistance salmonellae (Alam et al, 1995) and quinolones also have significantly reduced failure rates compared with some first-line agents in enteric fever caused by susceptible isolates (Thaver et al, 2008). Unfortunately, over the past decade, isolates with decreased ciprofloxacin susceptibility have become more common and are associated with treatment failure and relapse (Chuang et al, 2009). At the Hospital for Tropical Diseases, London, salmonellae with decreased ciprofloxacin susceptibility comprised 65% of all enteric fever isolates between 2000 and 2009 (Patel et al, 2010). For this reason, intravenous ceftriaxone is now the first-line agent when intravenous therapy is required and there is an epidemiological risk of quinolone resistance.

More recently, oral azithromycin has been shown to be effective (Girgis et al, 1999) and this is now the treatment of choice for uncomplicated enteric fever where decreased ciprofloxacin susceptibility is a risk (Effa and Bukirwa, 2008). Although there are no published breakpoints for azithromycin in *S. enterica* infections, European Committee on Antimicrobial Susceptibility Testing (2010) clinical breakpoint data refer to successful treatment of *S. typhi* isolates with minimal inhibitory concentration ≤16 mg/litre.

When considering salmonella infections that involve bone, the choice of antibiotic is further restricted by the bioavailability

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Case Report 1

A 16-year-old student presented to hospital with a 2-week history of back pain and fever which had developed while he was travelling in India. A week into his illness, he developed lower back pain and, at the time of presentation, his main complaint was of pain rather than fever. Physical examination was unremarkable except for lumbar and sacroiliac tenderness.

Routine testing revealed anaemia (haemoglobin 12 g/dl), leucocytosis (white cell count 10.5 x10^9/litre) and raised inflammatory markers (C-reactive protein 60 mg/litre, erythrocyte sedimentation rate 49 mm/hr). Renal and liver function tests were all normal. Culture of peripheral blood was sterile at 5 days on three occasions but *Salmonella paratyphi* A was isolated from stool. The organism was susceptible to amoxicillin, ceftriaxone and chloramphenicol but resistant to nalidixic acid and had decreased susceptibility to ciprofloxacin (minimal inhibitory concentration by E-test: ciprofloxacin 0.75 mg/litre, azithromycin 16 mg/litre).

Plain radiographs and magnetic resonance imaging of the spine revealed no pathology and the patient was treated with azithromycin 1 g daily for 10 days. However, his back pain worsened and a repeat magnetic resonance scan, 23 days after the first, showed L3–4 discitis and an associated extradural abscess. *S. paratyphi* was cultured from fluid aspirated from the abscess. 16S polymerase chain reaction analysis on the fluid also confirmed the presence of Salmonella-specific DNA and the absence of other bacterial genetic material.

He completed a 6-week course of intravenous therapy, initially amoxicillin then once-daily ceftriaxone. This was followed by 6 weeks of combination oral 2 g amoxicillin three times daily and azithromycin 1 g daily (the latter reduced to 1 g on alternate days after 2 weeks). Following completion of therapy, biochemical and radiological abnormalities have resolved, with minor residual sclerotic change and loss of disc height only. He remains well 2 years after treatment.

Case Report 2

A 23-year-old student developed fever, watery diarrhoea and vomiting while travelling in south-east Asia. One week after the onset of symptoms, she attended a local clinic and received a 3-day course of oral trimethoprim-sulfamethoxazole for a suspected urinary tract infection. Her symptoms did not resolve and 3 days later she presented to hospital with fever. Physical examination was unremarkable. Initial investigations showed an alanine aminotransferase level of 158 IU/litre and a C-reactive protein level of 146 mg/litre. The white cell count was normal (8.1 x10^9/litre). Ultrasound of the abdomen showed no abnormalities. She was admitted and treated for presumed bacterial gastroenteritis with intravenous ciprofloxacin and fluids. Afterr 2 days she was discharged on oral ciprofloxacin.

Five days later, she attended hospital in the UK complaining of persistence of fever and diarrhoea. No localizing features were recorded. Routine blood analysis was normal except a C-reactive protein of 91 mg/litre. No abnormalities were found on a contrast-enhanced computed tomography scan of the chest, abdomen and pelvis. She was empirically treated with meropenem 1 g three times daily and oral metronidazole 400 mg three times daily and transferred to the authors' hospital.

Twenty four hours later, *Salmonella typhi* (resistant to amoxicillin, chloramphenical, trimethoprim-sulfamethoxazole and nalidixic acid and with decreased susceptibility to ciprofloxacin – minimal inhibitory concentration by E-test: ciprofloxacin 0.25 mg/litre, azithromycin 6 mg/litre) was cultured from blood and her antibiotic therapy was changed to ceftriaxone 2 g twice daily. The fever initially settled but recurred 5 days later, at which time she also developed left-sided hip pain. Ultrasound scanning showed a joint effusion and 20 ml of straw-coloured fluid was aspirated. This was sterile on culture but sequencing of 16S ribosomal RNA gene polymerase chain reaction products revealed Salmonella-specific DNA. Osteomyelitis of the femoral head was demonstrated on magnetic resonance imaging. She was treated with intravenous ceftriaxone for 6 weeks and received azithromycin 1 g once daily starting 2 weeks after ceftriaxone and continuing for a total of 10 weeks. She made an uneventful recovery.

of agents at this site. There are no controlled studies to guide antimicrobial choice although there are individual reports of success with chloramphenicol, ampicillin/amoxicillin, third generation cephalosporins and quinolones. Ciprofloxacin has good penetration into bone (Fong et al, 1986) and is an effective agent in osteomyelitis caused by enterobacteriacae (Lew and Waldvogel, 1995), although most reports of its use in salmonella osteomyelitis document long-term administration as follow up to parenteral therapy with another agent. Whatever agent is used, the duration of therapy appears to be very important. In the most comprehensive review of salmonella vertebral osteomyelitis, relapse was found to be fairly common (9%) and the mean duration of antibiotic treatment in patients who were cured was 60 days (Santos and Sapico, 1998).

Like ciprofloxacin, azithromycin has excellent penetration into bone, with bone concentrations more than 30 times greater than serum concentrations (O'Reilly et al, 1992; Landersdorfer et al, 2009). Despite this, an experimental model of staphylococcal osteomyelitis showed that azithromycin had little effect on final bacterial counts in bone when used alone (O'Reilly et al, 1992). The same study did, however, show that the addition of azithromycin to clindamycin or rifampicin monotherapy significantly improved cure rates. The activity of azithromycin in bone against *Staphylococcus aureus* therefore remains unclear.

Conclusions

The choice of antibiotic was guided by the resistance phenotype. There is good evidence to support the use of azithromycin in uncomplicated enteric fever and it is known to penetrate bone well. The successful outcomes in these cases indicates that azithromycin as oral 'follow-on' therapy may have a role in the treatment of salmonella osteomyelitis caused by an organism resistant to other agents, or where the use of alternatives is precluded by hypersensitivity or drug availability. **BJHM**

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LEARNING POINTS

- Osteomyelitis is an uncommon, but not rare, complication of typhoid fever.
- The prevalence of antibiotic resistance in salmonellae is increasing.
- Azithromycin has been successfully used as an oral follow-on agent in the treatment of two cases of quinolone-resistant typhoid osteomyelitis.