Learning points

- ERCP is of value in the diagnosis of duct transection
- Complete pancreatic necrosis may occur leaving the duct intact

acute pancreatitis.⁴ However Sivit and colleagues suggested that this method was unreliable for assessing blunt pancreatic trauma in children as was our experience in the present case.⁵ This discrepancy may be due to the evolution of the pancreatic necrosis in relation to the timing of the imaging and subsequent surgery.

One of the major clinical questions in panc-

reatic trauma is whether the injury has produced duct transection and some authors have suggested that decisions on the necessity for surgery and its nature can be guided by ERCP findings.² This case has clearly shown that ERCP findings may also be misleading and that an area of complete pancreatic necrosis may occur whilst the duct crossing that segment of pancreas appears intact. Since the pancreatic duct is prone to division in severe pancreatic trauma,⁶ this situation may be due to the pancreatic duct's resilience to digestion by activated pancreatic enzymes.⁷

We would conclude that ERCP is of value in the diagnosis of duct transection but that an intact duct at ERCP does not relate to pancreatic viability or the surgical procedure necessary in treatment.

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Endocarditis due to high-level gentamicin-resistant *Enterococcus faecalis*

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Summary
We report a case of aortic valve endocarditis caused by *Enterococcus faecalis* highly resistant to gentamicin, which failed to respond to conventional antibiotic combination therapy. Extensive *in vitro* testing was required to determine an appropriate antimicrobial regimen. Despite bacteriological resolution and cardiac surgery the patient died from complications of infective endocarditis.

Keywords: *Enterococcus faecalis*, endocarditis

Introduction

Enterococci are intrinsically relatively less susceptible to penicillin and other cell-wall-active agents, including vancomycin and teicoplanin.¹ They are also intrinsically relatively resistant to aminoglycosides. However, the combination of penicillin (or vancomycin) with an aminoglycoside achieves a synergistic bactericidal effect, and is the established antibiotic regimen for the successful treatment of enterococcal endocarditis. The first case of endocarditis caused by a high-level

gentamicin-resistant (HLGR) enterococcus was reported in 1984 from the US.² Since then, nine such cases, including two in the UK, have been reported and recently reviewed by Moellering.³ This is only the third reported case of endocarditis caused by a HLGR *Enterococcus faecalis* in the UK.

Case report

A 40-year-old man was admitted with a two-month history of fever, night sweats, rigors and a painful leg. On examination, he had a fever of 38.6°C, signs of aortic regurgitation, finger clubbing, anaemia, two scrotal abscesses and deep vein thromboses in both calves clinically. Echocardiography confirmed aortic regurgitation and detected vegetations on the aortic valve. The clinical diagnosis of infective endocarditis was confirmed with the isolation of *E faecalis* in five sets of blood cultures. Treatment was initiated with intravenous benzylpenicillin (2 mega-units every four hours) and gentamicin (dosage determined by serum levels). Ciprofloxacin (400 mg twice daily) intravenously was substituted for gentamicin when HLGR was detected. Pus from the scrotal abscesses grew the same organism. Despite initial resolution of fever with negative

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blood cultures, the patient developed a dense left hemiparesis, a recurrent fever and atrial flutter 10 days later. Computed tomography revealed a right hemisphere infarct consistent with an embolic event. Tests of serum bactericidal activity proved unfavourable and blood cultures obtained five days earlier during penicillin and ciprofloxacin treatment grew *E faecalis* again. After extensive bacteriological testing, therapy was changed to a combination of intravenous high-dose ampicillin (2 g four hourly) and ciprofloxacin. Serum bactericidal titres on this regimen were satisfactory with negative blood cultures over the subsequent six weeks and the scrotal abscesses healed completely. Valve replacement was performed towards the end of this period for sudden gross haemodynamic decompensation and further embolic events. At surgery, a bicuspid aortic valve and a very large mobile vegetation were noted. A 13Å Starr–Edwards valve was inserted and antibiotic therapy continued for a further six weeks post-operatively. Unfortunately, the patient made little recovery from the cerebrovascular accident and died from its complications.

Bacteriological methods

The patient's blood was cultured in BACTEC blood culture medium. Material obtained from the aortic vegetations was inoculated onto chocolate and blood agar and incubated aerobically (5% carbon dioxide in air) and anaerobically. The remaining tissue underwent enrichment culture in thioglycollate broth and was then subcultured onto chocolate and blood agar and incubated as above. All isolates were identified by routine laboratory methods⁴ and confirmed by the PHLS Streptococcal Reference Unit at Colindale. Antibiotic susceptibility testing was performed using the comparative diffusion method⁵ and screening for HLGR was performed with 100 µg gentamicin discs.⁶ Minimum inhibitory (MIC) and bactericidal concentrations (MBC) of various antibiotics were determined by a macrodilution technique and different antibiotic combinations were assessed using the tambour transfer method.⁷ Serum bactericidal assay was performed as previously described.⁷

Results

Blood cultures before and during treatment with penicillin and ciprofloxacin grew group D streptococcus which was also isolated from the scrotal abscess pus. Isolates were later identified as *E faecalis* serotype 9, phage type X by the PHLS Streptococcus Reference Unit. Serum bactericidal tests after 10 days of penicillin with gentamicin therapy showed trough and peak titres of only 1 and 2, respectively, compared with 8 and 32, respectively, with ampicillin and ciprofloxacin treatment. Cultures of aortic valve and vegetations proved sterile.

Using the comparative disc diffusion method, the isolate was shown to be resistant to gentamicin, amikacin, erythromycin, tri-

methoprim, clindamycin, and chloramphenicol but sensitive to ampicillin and ciprofloxacin. MIC and MBC studies confirmed multi-drug resistance, including high-level resistance to gentamicin and streptomycin. Antibiotic combination assessments showed indifference, with no synergy or antagonism of action between ciprofloxacin and penicillin or ampicillin.

Discussion

High-level aminoglycoside resistance (MIC > 1000 mg/l) in enterococci is mediated via aminoglycoside-modifying enzymes encoded on various plasmids.⁸ A bifunctional enzyme, identical to that in gentamicin-resistant staphylococci, mediates high-level resistance to all currently available aminoglycosides except streptomycin. Plasmids encoding for HLGR frequently carry other determinants encoding resistance to many other antibiotics further limiting therapeutic options.

The immense potential for acquiring and disseminating resistance genes have enabled enterococci to become formidable nosocomial pathogens and have made effective treatment very difficult, particularly in endocarditis, as exemplified by this case report. High-level aminoglycoside resistance precludes the synergistic bactericidal activity between cell-wall-active antibiotics and aminoglycosides, crucial in the successful treatment of serious enterococcal sepsis in 'protected' sites such as heart valve vegetations and the meninges. On their own, β-lactam antibiotics (penicillin, ampicillin) and glycopeptide antibiotics (vancomycin, teicoplanin) are only bacteriostatic against enterococci.

To date, only 10 cases of endocarditis caused by HLGR enterococci have been reported. Of these, one died without treatment and one did not have high-level streptomycin resistance and was cured with penicillin/vancomycin with streptomycin. Of the remaining eight, only three were cured by antibiotics alone – two with ampicillin and one with vancomycin. Relapse or primary failure of antibiotic therapy occurred in the other five patients – one died and four were cured after cardiac surgery.

The optimum treatment for endocarditis caused by HLGR enterococci is presently unknown. The choice of antibiotics depends on extensive *in vitro* testing and *in vivo* monitoring of clinical efficacy. Rarely, when HLGR is dissociated from high-level streptomycin resistance, streptomycin can be used in combination with a cell-wall-active agent. Ampicillin demonstrates greater, though still incomplete, bactericidal activity than penicillin. Amongst the glycopeptide antibiotics, teicoplanin is about 2–4 times more active than vancomycin against enterococci *in vitro*.

Macrolides, tetracyclines and rifampicin are bacteriostatic against enterococci and rifampicin resistance develops rapidly. Enterococci are resistant to trimethoprim–sulphamethoxazole *in vivo*. Among the fluoroquinolones, ciprofloxacin inhibits enterococci at concentrations near the maximal attainable serum levels.

Endocarditis due to gentamicin-resistant *Enterococcus faecalis*

- consider valve replacement early
- iv ampicillin (12 g/day for six weeks)

Newer fluoroquinolones such as sparfloxacin show improved *in vitro* activity against enterococci and may be more effective in enterococcal endocarditis. Other investigational agents including lipopeptides (daptomycin)⁹ and streptogramins (pristinamycin)¹⁰ show bactericidal activity *in vitro* and may prove clinically useful.

In conclusion, until effective antimicrobial treatment for endocarditis due to HLGR enterococci is established, we recommend that serious consideration be given to cardiac surgery to effect cure, as commonly available antibiotics are primarily bacteriostatic against this organism. Large intravenous doses of penicillin (ampicillin 12 g daily in six divided doses for patients with normal renal function) should be given for six weeks. Glycopeptide antibiotics can be used in patients allergic to

β -lactam antibiotics or infection with β -lactam-resistant enterococci. Teicoplanin may be preferable to vancomycin if renal function is impaired. Decisions to use additional antibiotic combinations must be based on extensive *in vitro* testing but it should be appreciated that *in vitro* synergy may not guarantee *in vivo* success. This case also illustrates the significant role the laboratory can play in the management of serious infection.

Antibiotic susceptibility of the organism was confirmed by Dr R George of the Antimicrobial Reference Laboratory and full identity of the isolates established by Dr D Morrison of the Streptococcal Reference Unit, Central Public Health Laboratory, Colindale, UK. We thank Dr C Pumphrey for permission to report this case and Miss Dawn Vallance for expert secretarial assistance.

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