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(Accepted 16 July 1998)

Antibiotic resistance among enterococci causing endocarditis in the UK: analysis of isolates referred to a reference laboratory

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Enterococci account for 5-15% of cases of bacterial endocarditis.¹ They are the most resistant bacteria commonly encountered in this type of infection, which is still associated with a mortality of 20-30%.² The treatment regimen for enterococcal endocarditis recommended by the British Society for Antimicrobial Chemotherapy and the American Heart Association is a synergistic bactericidal combination of a penicillin or glycopeptide with an aminoglycoside, usually gentamicin or streptomycin.^{3,4} However, enterococci can acquire high level resistance to aminoglycosides, which abolishes this synergy.¹ Enterococci can also exhibit high level resistance to penicillin or to glycopeptides.¹ Our laboratory undertakes testing of bacteria from cases of endocarditis as a routine service; we analysed resistance among isolates from 120 cases of enterococcal endocarditis, received over 27 months.

Methods and results

Results of tests for antibiotic susceptibility were analysed for enterococci referred from patients with a clinical diagnosis of endocarditis between January 1995 and March 1998. Isolates exhibiting high level resistance to gentamicin or streptomycin were defined as those where the concentration of antibiotic required to inhibit growth on laboratory media (minimum inhibitory concentration) exceeded 2000 mg/l.¹ Resistance to other antibiotics was defined according to criteria specified by the British Society for Antimicrobial Chemotherapy.⁵

The isolates, which were from 60 UK hospitals, comprised 106 *Enterococcus faecalis*, 13 *E faecium*, and one *E avium*. The table shows the major resistance characteristics of these isolates. Overall, 26% of isolates had high level resistance to both gentamicin and streptomycin (22% of *E faecalis* isolates; 62% of *E faecium* isolates). A further 28 *E faecalis* isolates showed high

level resistance to either gentamicin (7 isolates) or streptomycin (21 isolates); four *E faecium* isolates and the sole *E avium* isolate showed high level resistance to streptomycin but not to gentamicin.

All the *E faecalis* isolates remained susceptible to ampicillin (minimum inhibitory concentration 0.5-4 mg/l for 105 isolates and 8 mg/l for 1 isolate), but 6 were resistant to vancomycin, with 2 exhibiting cross resistance to teicoplanin. One isolate resistant to glycopeptides also had high level resistance to both gentamicin and streptomycin. The 13 *E faecium* isolates were all resistant to ampicillin (>8 mg/l), with 3 also resistant to vancomycin but not teicoplanin. Two of these vancomycin resistant isolates showed high level resistance to gentamicin and streptomycin.

Comment

Treatment for enterococcal endocarditis comprises a bactericidal synergistic combination of a penicillin (usually ampicillin or benzylpenicillin) or glycopeptide with an aminoglycoside, usually gentamicin or streptomycin for at least 4 weeks.^{2,3} It is therefore disturbing

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BMJ 1998;317:629-30

Resistance of enterococci from 120 cases of endocarditis to aminoglycosides and to cell wall active antibiotics

Antibiotic	No (%) of isolates showing resistance			
	All species (n=120)	<i>E faecalis</i> (n=106)	<i>E faecium</i> (n=13)	<i>E avium</i> (n=1)
Aminoglycosides:				
Gentamicin and streptomycin	31 (26)	23 (22)	8 (62)	0
Gentamicin only	7 (6)	7 (7)	0	0
Streptomycin only	26 (22)	21 (20)	4 (31)	1
Neither aminoglycoside	56 (47)	55 (52)	1 (8)	0
Cell wall active agents:				
Ampicillin	13 (11)	0	13 (100)	0
Vancomycin and teicoplanin	2 (2)	2 (2)	0	0
Vancomycin, but not teicoplanin	8 (7)	4 (4)	3 (23)	1

that 26% of the enterococci in this study were highly resistant to both gentamicin and streptomycin. Aminoglycosides have no therapeutic benefit in infections involving such strains, and unnecessarily expose patients to possible ototoxic or nephrotoxic side effects. A further 28% of the isolates were highly resistant to either gentamicin or streptomycin, emphasising the value of testing both of these compounds in determining appropriate treatment.

Current guidelines recommend that endocarditis caused by enterococci with high level resistance to aminoglycosides should be treated with high dose amoxycillin or ampicillin for 6-12 weeks.^{2,3} However, 11% of the enterococci were *E faecium*, which typically is resistant to ampicillin. Moreover, amoxycillin or ampicillin would be unsuitable for patients allergic to penicillin. This latter constraint applies to other proposed regimens that combine ampicillin with imipenem or ciprofloxacin. Although glycopeptides may be considered in place of penicillin, the finding of glycopeptide resistance in several isolates, including three of the *E faecium* isolates, means that their efficacy cannot be guaranteed.

The picture revealed is disturbing, with frequent resistance to the recommended synergistic combinations. Evaluation in endocarditis of unconventional regimens—for example, ampicillin plus carbapenems, ampicillin plus ciprofloxacin, or ciprofloxacin plus co-trimoxazole—is desirable, although the use of such

broad spectrum agents may risk selecting resistance in the body microflora. Also desirable is early evaluation, in endocarditis, of novel narrow spectrum anti-Gram positive agents, such as streptogramins, oxazolidinones, and evernimomycins.

We thank Dr Ty Pitt and his colleagues in the Epidemiological Typing Unit at the Laboratory of Hospital Infection in the Central Public Health Laboratory for confirming the species of the isolates studied.

Contributors: APJ and DML jointly conceived the idea for the project. APJ analysed the data and drafted and edited the paper. MW performed the antibiotic susceptibility tests and contributed to the writing. DCE, NW, and DML contributed to the discussions on interpretation of the data and writing of the paper.

Funding: Public Health Laboratory Service.

Competing financial interest: APJ and DML have received financial support from Rhône-Poulenc Rorer for work on novel streptogramins and for attending conferences.

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(Accepted 7 August 1998)

Multidrug resistant tuberculosis in France 1992-4: two case-control studies

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BMJ 1998;317:630-1

Since 1988 several outbreaks of multidrug resistant tuberculosis have occurred in the United States and Europe. We surveyed the national network of laboratories serving 80% of public hospital beds in France to measure the prevalence of multidrug resistant tuberculosis during 1992-4.¹

Subjects, methods, and results

Annual prevalence of multidrug resistance was calculated by dividing the number of cases of multidrug resistant tuberculosis—patients who had at least one isolate resistant to isoniazid and rifampicin in the calendar year—by the total number of cases with tuberculosis confirmed by culture that the laboratories reported. Multidrug resistant tuberculosis was defined as secondary in patients who had been treated for 1 month or more before the first known multidrug resistant isolate, and as primary in all other cases. DNA fingerprinting was performed on multidrug resistant strains sampled in 1993 and 1994.² Factors associated with multidrug resistant tuberculosis were analysed by comparing cases of multidrug resistant tuberculosis reported by the laboratories with cases that were noti-

fied for the same period by 69 (of 100) French districts where HIV infection was consistently monitored. We compared primary and secondary cases of multidrug resistant tuberculosis in two case-control studies with all notified new cases and all notified cases with a history of previous tuberculosis respectively. We performed multivariate analysis by logistic regression.

In 1992, 48 out of 8521 cases of tuberculosis confirmed by culture were multidrug resistant (0.6% (95% confidence interval 0.4% to 0.7%)); in 1993, 40 out of 8539 (0.5% (0.3% to 0.6%)); and in 1994, 58 out of 7752 (0.7% (0.5% to 0.9%)) (P=0.10 for trend). Prevalence did not vary significantly between the 22 administrative regions.

The 146 cases occurred in 125 patients, of whom 116 (93%) had pulmonary tuberculosis (70 had a positive sputum smear test). Of 122 patients with information on previous treatment, 31 had primary and 91 secondary multidrug resistant tuberculosis. Overall, 91 out of 122 (74%) of the patients were men and 58 out of 122 (49%) were born outside Europe, without significant difference between primary and secondary cases. Primary cases were significantly younger than secondary cases (median age 35 years v