Genotyping confirmed that all 48 isolates expressed the \textit{vanA} gene. The distributions of the MICs of LY333328, teicoplanin and vancomycin for the strains are shown in the Table. The MICs of LY333328 were significantly lower than those of both teicoplanin and vancomycin (Wilcoxon matched-pairs signed-ranks test, \( P < 0.05 \)); teicoplanin was more active than vancomycin. The MIC\(_{50}\) of LY333328 was 0.25 mg/L, which was four-fold lower than that (1 mg/L) for clinical isolates of vancomycin-resistant \( \textit{E. faecium} \) recently reported by Schwalbe \textit{et al.} in the USA.\(^6\) The ranges of MICs for the strains of animal and human origin in this study were similar, an observation that is consistent with the food chain having been the route of transmission.

Our results confirm that LY333328 could potentially be used to treat infections caused by VRE in both animals and humans. Since avoparcin was the most frequently administered growth promoter for animals involved in food production in The Netherlands, until a ban on its use was imposed, the results also suggest that this antibiotic does not select for resistance to LY333328. Finally, it appears that enterococcal isolates from the faeces of healthy animals and humans could be used as indicators of antibiotic resistance, the control of which is crucial to our ability to treat infected patients effectively in the future.

### References


### Correspondence

**Vancomycin-dependent enterococci: curious phenomenon or serious threat?**

\textit{J Antimicrob Chemother} 1997; 40: 734–735

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Sir,

Vancomycin dependence amongst enterococci is a recent observation\(^1\) that has attracted media attention and sparked medical debate.\(^2–5\) Fears have been expressed that the acquisition of vancomycin dependence represents the advent of the ‘superbug’\(^2\) and that it is far more common than the sparse published reports suggest.\(^3\) Given the issues involved, the potential clinical impact and the emotive nature of the phenomenon, we considered it important to quantify the genuine risks posed by this development.

Our first vancomycin-dependent enterococcus (VDE) was recently isolated from a 36 year old male patient with end-stage renal failure secondary to diabetic nephropathy who had been haemodialysed via a central venous catheter since 1995. His clinical course was complicated by recurrent episodes of line-related bacteraemia, initially caused by coagulase-negative staphylococci. Subsequently, methicillin-resistant strains of \textit{Staphylococcus aureus} (MRSA) were isolated on at least three occasions and, between July and September 1996, vancomycin-susceptible strains of \textit{Enterococcus faecalis} (VSE) were recovered from blood cultures, again on three separate occasions. In the light of the antimicrobial susceptibilities of the aetiological agents, intravenous (iv) vancomycin became an integral component of the treatment regimen and was administered frequently over a relatively short period.

On two occasions in November and December 1996 respectively, vancomycin-resistant strains of \textit{E. faecalis} (VRE) were isolated from blood cultures obtained because of suspected line-related infections. The treatment regimen comprised iv amoxicillin (to which the isolates were susceptible) and vancomycin; the MICs of vancomycin and teicoplanin for the isolates were >1024 mg/L and >32 mg/L respectively. In January 1997, during a further febrile episode, blood cultures again yielded a strain of \textit{E. faecalis} which was noted to be growing perfusely around the vancomycin disc, but sparsely elsewhere on the susceptibility test plate. An Etest (Cambridge Diagnostics Ltd) was used to confirm the organism’s dependence on vancomycin for growth. Although a small number of other colonies grew at a distance from the vancomycin strip, serial subculture of dependent colonies consistently produced this same growth pattern.

Restiction endonuclease analysis with SaI digestion\(^6\) of
Correspondence

DNA extracted from seven enterococci isolated from this patient over a 7 month period (three VSE, two VRE, the VDE and a non-dependent peripheral colony growing on the same plate as the VDE) demonstrated that they were virtually indistinguishable (data not shown).

Our observations suggest that the repeated use of vancomycin in this patient resulted in progression of the same enterococcal strain from vancomycin susceptibility, first to vancomycin resistance and subsequently to vancomycin dependence, i.e. acquisition by a vancomycin-susceptible strain of a vancomycin resistance determinant, rather than acquisition of a second vancomycin-resistant strain. Moreover, the antibiotic failed to eradicate the organism, but selected a genotypic expression that conferred a survival advantage, a development that may eventually pose a threat to the wellbeing of the host. On the other hand, the phenomenon of vancomycin dependency is unlikely to be anything more than the facilitation of growth of a mutant isolate in the presence of the antibiotic. There is, to date, no evidence that vancomycin dependence represents any more of a concern than vancomycin resistance, with the possible exception that it might lead to the failure to detect VDE on normal culture media. In the case reported here, however, this would have been unlikely as repeated sub-culture of the VDE consistently resulted in growth of resistant colonies distant from the vancomycin disc/strip; these colonies were presumably revertants from dependence and have been described previously. Rather, it seems that mutation to vancomycin dependence does indeed represent an ‘evolutionary dead-end’ because it is lethal in the absence of the antibiotic.

There are, however, other concerns that we consider to be of greater importance than the ‘discovery’ of vancomycin dependence. This department has recently isolated VRE from 17 patients, six (35%) of whom were co-infected with MRSA. Given the on-going and unavoidable use of vancomycin as therapy of patients with invasive infections caused by MRSA, it was not surprising that the incidence of isolating VRE has risen. Not only does this epidemic constitute an immediate health risk, owing to the difficulty in effectively treating patients infected with these organisms, but, looking to the future, the co-existence of VRE and MRSA in the same patient poses the greatest threat yet of the in-vivo transfer of genetic material encoding vancomycin resistance to MRSA, with the advent of a highly virulent and currently untreatable pathogen—a genuine ‘superbug’.

Acknowledgement

The case reported here is presented with the kind permission of the Renal Unit at the Royal London Hospital.

References


Changes in antimicrobial resistance of enterococci isolated in Greece


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Sir,

Enterococci have emerged as important nosocomial pathogens, particularly in hospitals where cephalosporins are used at large. For serious enterococcal infections, the combination of a cell wall active antibiotic (such as ampicillin or vancomycin) plus an aminoglycoside remains the most suitable therapeutic choice. However, such infections become difficult to treat when resistance to these emerges. We have previously reported trends in susceptibility to these antimicrobials among enterococci isolated during 1993–94 from clinical infections in northern Greece. In that study, relatively high rates of antibiotic resistance were detected for all compounds tested and a considerable number of enterococci were found to produce β-lactamases.

In the present report, of strains isolated from the same hospital setting during 1996–97, we have estimated changes in susceptibility to antibiotics among enterococcal strains responsible for clinical infections. A total of 151 Enterococcus faecalis and 38 Enterococcus faecium non-repetitive strains were consecutively isolated at AHEPA University Hospital, one of the largest hospitals in northern Greece. Identification to species level was performed using a conventional test scheme, and a microdilution method, with Pasco MIC Gram-positive panels (Difco Laboratories, Detroit, MI, USA), was used to determine their susceptibility to a range of antimicrobials. Susceptibility status was defined according to NCCLS guidelines. Isolates were