Comment on: Intensive care unit dissemination of multiple clones of linezolid-resistant Enterococcus faecalis and Enterococcus faecium

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Sir,

We read with interest the recent article by Ntokou et al.1 that describes the multiclonal spread of linezolid-resistant (LR) Enterococcus faecium and Enterococcus faecalis in the intensive care unit (ICU) of the University Hospital of Larissa (UHL), Central Greece, during 2007–08. The article raises several issues that could be discussed. In the Discussion section it is stated that, ‘in Greece, where multidrug resistance is increasing, linezolid resistance remains rare and there is only one study reporting five LR enterococci colonizing patients in a single ward, with four of the isolates being clonally related.’1 Surprisingly, the authors refrain from discussing any other previous Greek studies by Mitsogiannis et al.,2 Pratti et al.,3 or Spiliopoulou et al.,4 which would have provided the reader with a broader view on linezolid resistance in our geographical region. Published data corroborate the observation that while the first LR E. faecium isolate had emerged in the ICU of UHL in 2004,4 it was followed, 8 months later, by an LR E. faecalis that firstly colonized and then caused a urinary tract infection in a patient previously hospitalized in this ICU.2 During 2005, a multicentre study conducted in seven hospitals throughout the country showed that among 1100 enterococcal isolates tested (700 E. faecalis and 400 E. faecium), 19 (1.72%, 12 E. faecalis and 7 E. faecium), all recovered from infected sites, were resistant to linezolid.7 Dissemination of LR enterococci in Greek ICUs has been also reported,4 between April and June 2009, LR enterococci disseminated in six Greek ICUs and caused infections. Hence, the data do not support the statement ‘linezolid resistance remains rare’ in Greece.

Previous studies have demonstrated that there is a strong correlation between the ratio of mutated to total alleles and linezolid MIC values.5 MICs are highest, up to 64 mg/L, for mutants homozygous for T2576 in their 23S rRNA genes.5 In contrast, all isolates described by Ntokou et al.1 exhibited low-level resistance to linezolid (MICs 8–16 mg/L) irrespective of their homogeneous or heterogeneous allelic profiles. Such an unexpected finding would at least require determination of the allelic profiles by a method more appropriate than the ‘careful examination of the sequencing traces’.5 The digestion of 23S rRNA PCR products by NheI is a simple and rapid method to distinguish homozygous from heterozygous profiles: the G2576T mutation, which is mainly associated with the expression of linezolid resistance in clinical isolates, introduces a restriction site for the restriction endonuclease NheI.5 Moreover, several more robust methods have been proposed (pyrosequencing, etc.) to estimate the numbers of native and mutated 23S rRNA gene copies.4,5 Microbiological laboratories that do not have the infrastructure to carry out pyrosequencing usually perform separate PCR amplification of the different copies of the 23S rRNA followed by sequence analysis. For each copy, specific primers could be designed based on the published E. faecalis V583 genome (GenBank accession number AE016830) and E. faecium genome (GenBank accession number NC_017022).4 The choice of the typing method to investigate the epidemiology of LR enterococci should primarily be dictated by the timescale being examined and the aims of the investigation. In the course of hospital outbreak investigations, a short timescale is examined, and methods of high discriminatory power are preferable. PFGE typing is the method that has been most commonly applied in such settings. Multilocus sequence typing (MLST) is less discriminatory than PFGE and would be more suitable to large-scale longitudinal surveillance. In the article by Ntokou et al.,1 the authors support the view of a multiclonal composition of LR enterococci during 2007–08, based on PFGE results. However, during a 2 year period, it is possible that isolates assigned to the same index strain had distinct pulstotypes due to frequent rearrangements that occur in enterococci.7 Consequently, differences in PFGE patterns should be interpreted more cautiously. In 2009, Spiliopoulou et al.4 demonstrated that in six Greek ICUs (including the ICU of UHL), LR E. faecium were clonally related and belonged to the international epidemic clones ST16, ST17, ST65 and ST203, while all LR E. faecalis belonged to ST28. For that reason, to support the multiclonal composition as well as the evolutionary scenario proposed by Ntokou et al.1 that ‘the multiclonal composition of the LR isolates indicates that linezolid resistance emerged on several independent occasions and patient-to-patient transmission was not the main route of dissemination’, representative PFGE clusters of E. faecalis and E. faecium should have been characterized by MLST and compared with those described in other national and international studies.

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Sir,

The new endocarditis treatment guidelines of the BSAC published in JAC recommend the fluoroacillin and rifampicin combination as the treatment of choice for prosthetic valve bacterial endocarditis.1 We have some concerns about this recommendation. Although the use of anticoagulants in the treatment of infective endocarditis is controversial due to an increased risk of intracranial haemorrhage, there are critical points about thromboembolic events in patients with prosthetic valve infective endocarditis. A meta-analysis of nine studies that evaluated cerebrovascular accidents, including both haemorrhagic and ischaemic events, associated with anticoagulant use in prosthetic valve infective endocarditis, showed not only no increased risk of haemorrhagic stroke in anticoagulated patients, but also a 4-fold decreased risk of ischaemic stroke.2 In the absence of a consensus statement concerning these two types of cerebrovascular accidents in patients with prosthetic valve infective endocarditis, many practitioners prefer to reconsider anticoagulants soon after the initiation of antibiotic therapy and valve replacement in these patients.

There are few reports of anticoagulant (warfarin) resistance following administration of penicillinase-resistant penicillins (PRPs), including nafcillin, dicloxacillin and flucloxacillin.3–6 The exact mechanism of this interaction has not been fully defined, but increased warfarin metabolism through non-specific enzyme induction with nafcillin has been described.7 In most of these reports, the effects of this interaction initiated within a few days and lasted for 10–15 days after PRP antibiotic cessation, and increased warfarin doses were unsuccessful in overcoming this resistance. Considering a 6 week duration of antibiotic therapy with oxacillins (recommended by the BSAC 2012 endocarditis guidelines1) and an additional 2 week period after the end of antimicrobial treatment, patients may remain unprotected against thromboembolic events associated with the prosthetic valves for an ~8 week period. In addition, due to an unpredictable pattern of warfarin response following oxacillin discontinuation, patients may be placed at increased risk of warfarin overdose after hospital discharge within 2 weeks.

There are few alternatives to warfarin in patients with prosthetic valves. Most of the alternatives are injectable (e.g. heparin and low-molecular-weight heparin) or high cost (e.g. dabigatran), while none of them is approved for this indication. Known antimicrobial alternatives for oxacillins in prosthetic valve bacterial endocarditis caused by Streptococcus spp. and methicillin-susceptible Staphylococcus aureus are first-generation cephalosporins. Interaction between cefazolin (an injectable first-generation cephalosporin) and warfarin is well defined and predictable. Cefazolin may increase the warfarin effect.7

In addition to these considerations, rifampicin itself is a potent inducer of warfarin metabolism and may increase the warfarin dosing requirement in >50% of situations, in order to achieve prothrombin time/international normalized ratio therapeutic goals. As with oxacillins, this effect may remain for >2 weeks after rifampicin discontinuation.8

In conclusion, many practitioners may encounter problems when managing the oxacillin/warfarin interaction and may prefer to not select oxacillins in the treatment of prosthetic valve bacterial endocarditis. It would possibly make it inconvenient to practice according to the BSAC 2012 endocarditis antimicrobial treatment guidelines in this specific category of patients, unless interactions between antibiotics and anticoagulant agents are fully considered.

Transparency declarations

None to declare.

References

1 Gould FK, Denning DW, Elliott TSJ et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the

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