Detection of glycopeptide resistance in Staphylococcus aureus

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Sir,

We have a number of comments regarding the recent letter from Aucken et al.1 describing a study of the incidence of GISA (glycopeptide-intermediate Staphylococcus aureus) in the UK using a number of different methodologies at different times.

The emergence of S. aureus with reduced susceptibility to glycopeptides (particularly vancomycin), whilst a significant threat also poses interesting challenges as regards definition and detection. The prototypical strain of GISA, Mu50,2 has a vancomycin MIC of 8 mg/L and is therefore by definition resistant using BSAC breakpoint criteria (it is intermediately resistant using NCCLS criteria). A second group of isolates have been described that have an MIC below the breakpoint (and therefore test as susceptible) but have a subpopulation of cells that can grow in the presence of vancomycin concentrations of ≥4 mg/L. These strains have been dubbed hVISA (heterogeneously vancomycin-intermediate S. aureus) or hGISA (heterogeneously glycopeptide-intermediate S. aureus). Aucken et al.1 only looked for GISA strains and we would suggest that this is not appropriate. In our experience of testing 12 GISA and 53 hGISA isolates from around the world, using population analysis profiles, GISA and hGISA are representative of a single resistance phenotype that is expressed as population heterogeneity in susceptibility to glycopeptides. There appears to be some variability in the vancomycin MIC between these strains that have a continuum of MICs ranging from 2 to 16 mg/L. It is only because these MICs straddle a somewhat arbitrary threshold of the breakpoint that strains from this phenotype are divided into GISA and hGISA. From the literature it is unclear whether GISA and hGISA can be separated in their clinical importance, since there are few systematic data regarding treatment outcomes in patients with infections, due to these isolates. It is quite possible that hGISA is a forerunner to GISA and when exposed to vancomycin, particularly for extended periods, can acquire the higher levels of resistance, permanently or otherwise. GISA strains reported in the literature have all been isolated from patients who have had prolonged courses of vancomycin for methicillin-resistant S. aureus (MRSA) infections. Typing of GISA isolates has shown them to be indistinguishable from the patient’s original MRSA strains, suggesting that resistance has developed in vivo during treatment (rather than acquisition of a new strain). The work of Sieradski et al.3 and Kurodo et al.4 indicates that multiple alleles are involved in producing the resistance phenotype and therefore the development of full resistance is likely to be a multi-stage process. This would support the assertion that hGISA strains may be precursors of GISA. For these reasons we would suggest that a study of the prevalence of S. aureus with reduced glycopeptide susceptibility should include both GISA and hGISA.

The methodologies being used in different countries to detect this type of resistance vary markedly. In Bristol, UK, we have evaluated most of the proposed methods to detect both GISA and hGISA. In our opinion, the most accurate of these is population analysis profiles–area underneath the curve (PAP–AUC).5 However, whilst this should be used as a confirmatory test in reference laboratories, it is relatively specialized and not appropriate for use by routine laboratories. Therefore, a simple screening method is required. We have evaluated the screening plate method, advocated by both CDC and Aucken et al.,1 and found it to be lacking in sensitivity. The use of the ‘macro-method’ using the Etest is one that is specifically designed to detect hetero-resistance as it allows detection of the resistant subpopulation after a 48 h period.6 To describe this as an MIC is incorrect; it is a method to detect a specific phenotype and should not be interpreted as the ‘level’ of resistance. According to the manufacturer (AB Biodisk, Solna, Sweden), the interpretative criteria for a hGISA/GISA when using this method is vancomycin ≥ 8 mg/L and teicoplanin ≥ 8 mg/L, or teicoplanin ≥ 12 mg/L. Furthermore, they emphasize that in-between two-fold values, e.g. 6 mg/L, must not be rounded up, for this specific procedure to maintain the window between GISA/hGISA and MRSA/MSSA. Using this interpretation, Oxford Staphylococcus NCTC 6571 and most MRSA and MSSA correctly fall into the non-GISA/hGISA category.

Aucken et al.1 seek to reassure clinicians that GISA is not a major problem in England and Wales and say that GISA is very rare or absent. We would agree that GISA is
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uncommon, although we note that the Public Health Laboratory Service reported ‘several isolates’ of MRSA from Southampton and Portsmouth earlier this year that were intermediately resistant to teicoplanin and therefore were GISA strains. These strains have a vancomycin MIC of 4 mg/L. In contrast to Aucken et al.,1 we would support the CDC recommendation of submitting S. aureus isolates with a vancomycin MIC of 4 mg/L to further study. This would be expected to identify GISA strains such as those from Southampton and Portsmouth. The suggestion that we should not investigate S. aureus strains with borderline MICs because there are so many of them (12.6% of isolates submitted to CPHL) is not tenable without further information on these strains, since this high rate could indicate a widespread problem with hGISA and could presage further problems with GISAs. It would be helpful to know whether any of these strains have the heterogeneous resistance phenotype and whether they are fully sensitive to teicoplanin.

There are many reasons why patients fail glycopeptide therapy and not all can be directly attributed to the bacteria’s response to the antibiotic. Therefore, we believe it is prudent to collect as much information as possible on both GISA and hGISA to accurately assess their true status within the clinical environment and to determine whether their in vitro phenotype can be linked to therapeutic failure. In our opinion, methods implemented in a screening system should detect both GISA and hGISA. Data collected from our UK screening studies would indicate that the level of hGISA is low (<1%) and that of GISA, even lower.

References