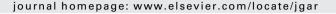
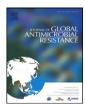


Contents lists available at SciVerse ScienceDirect

Journal of Global Antimicrobial Resistance





Review

Vancomycin in the treatment of meticillin-resistant *Staphylococcus aureus* (MRSA) infection: End of an era?

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ARTICLE INFO

Article history: Received 12 December 2012 Accepted 24 January 2013

Keywords: hVISA MIC creep VISA

ABSTRACT

Infection with meticillin-resistant *Staphylococcus aureus* (MRSA) continues to have significant morbidity and mortality. Vancomycin, which has been the mainstay of treatment of invasive MRSA infections, has several drawbacks related to its pharmacological properties as well as varying degrees of emerging resistance. These resistant subpopulations are difficult to detect, making therapy with vancomycin less reliable. The newer agents such as linezolid, daptomycin, ceftaroline, and the newer glycopeptides telavancin and oritavancin are useful alternatives that could potentially replace vancomycin in the treatment of certain conditions. By summarising the discussions that took place at the III MRSA Consensus Conference in relation to the current place of vancomycin in therapy and the potential of the newer agents to replace vancomycin, this review focuses on the challenges faced by the laboratory and by clinicians in the diagnosis and treatment of MRSA infections.

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1. Introduction

Meticillin-resistant *Staphylococcus aureus* (MRSA) remains a key pathogen both in community and hospital settings. Despite the availability of antimicrobial agents such as vancomycin and teicoplanin, and more recently linezolid and daptomycin, both morbidity and mortality from MRSA infections remain substantial [1,2]. The previous expert consensus conference, which took place in Florence, Italy, published a paper in 2012 [3]. This review is a summary of the discussions that took place at the International Society of Chemotherapy MRSA panel meeting held in Naples in March 2012.

The last few years have seen a surge in the availability of antimicrobial agents active against MRSA, e.g. linezolid, daptomycin, tigecycline, telavancin and ceftaroline. However, the spread of resistance determinants among MRSA has continued. Fortunately, there are still only a small number of reports of fully vancomycin-resistant MRSA. The spread of MRSA has been reduced in many areas of the world (e.g. the UK, USA), but serious MRSA infections often still result in poor outcomes [4]. Thus, there is a continuing need to develop newer, more effective antimicrobial agents and to explore strategies that may enhance the potency of existing agents. This may include pharmacokinetic/pharmacodynamic (PK/PD) modelling studies, the use of combination therapy, and revisiting the current breakpoints. Antimicrobial susceptibility testing and the use of genotypic tests for resistance gene detection need to be standardised and must include all appropriate resistance gene alleles (e.g. mecA and mecC). Bovine and human strains of MRSA isolated in Denmark and the UK were reported to carry a novel mecA homologue (originally published as LGA251 but now renamed *mecC*) in a novel type XI staphylococcal cassette chromosome. This allele was present in ca. 70% of mecAnegative MRSA isolates [5]. How widely this gene will spread still has to be determined. Further complicating antimicrobial susceptibility testing are reports of mecA-positive invasive isolates of S. aureus that appear to be susceptible to oxacillin by phenotypic testing [6]. Reasons for such discrepancies may include inducible oxacillin resistance and heteroresistance, or a non-functional mecA determinant owing to mutation. Such discrepancies may be rare but, given the large denominator of MRSA infections, their impact on clinical management could be significant.

2. Place of vancomycin in the treatment of MRSA

S. aureus has evolved from susceptibility to virtually all antimicrobial agents, including penicillin, to multidrug resistance, including resistance to the newer agents daptomycin and linezolid. This includes varying degrees of resistance, such as vancomycinintermediate *S. aureus* (VISA) and heteroresistant VISA (hVISA), that are a challenge both to laboratory detection and to clinical care. It is likely that the emergence of VISA from vancomycinsusceptible MRSA is a multistep process. VISA emerges from hVISA, a term that is not formally defined [7]. These phenotypic changes are orchestrated at the genetic level through a series of events [8].

A paper by Cafiso et al. underlines the complex genetic mechanisms that occur in the transition of vancomycin-susceptible MRSA to hVISA and VISA [9]. One mechanism of reduced susceptibility in VISA strains is a thickened cell wall. This is the end result of a process that is achieved either by producing excess cell wall precursors, by reduction in autolysis, or both [10]. The genetic mechanisms that underlie these alterations include loss of agr functions (the agr locus contains the hld gene encoding the δ -haemolysin) and alterations in atl, lytM and sceD, among others. Phenotypic changes include a high rate of cell wall turnover (enhanced expression of sceD) and a change to a positive surface charge (mprF upregulation). They result in reduced surface binding

of antimicrobial agents such as vancomycin and daptomycin. Further changes to the regulatory mechanisms that control cell wall autolysis (i.e. downregulation of atl and lytM) give rise to cells with the VISA phenotype. Moreover, antimicrobial agents can induce these responses. For example, daptomycin leads to upregulation of the mprF gene leading to its exclusion from the cell by the increase in cell wall positive charges. Daptomycinresistant mutants additionally demonstrate increased expression of the *dlt* operon, which increases the net surface charge on the cell. Acquisition of a positive surface charge in daptomycin-resistant cells is a dynamic process due to several mechanisms that operate in opposite directions. Mishra et al. hypothesised that the initial negative charge is a result of glutamate amidation on the cell surface, which leads to rapid entrapment of positively charged daptomycin molecules, followed by the overexpression of mprF (perhaps as a result of daptomycin-mediated induction) leading to acquisition of positive charges on the surface [11].

Whatever the genetic mechanisms, the ultimate biological outcome is reduced in vitro susceptibility to vancomycin. The extent to which these changes result in clinically relevant levels of resistance is uncertain, although cumulative data and opinion suggest that the utility of vancomycin in clinical practice may be limited as a result of these evolutionary changes. Thus, in an observational study of 1994 episodes of bacteraemia due to either MRSA or meticillin-susceptible S. aureus (MSSA), treatment with a glycopeptide was an independent predictor of higher mortality irrespective of meticillin resistance [12]. However, a substudy of 532 episodes found that mortality was significantly higher if the vancomycin E-test minimum inhibitory concentration (MIC) of the causal isolate was >1.5 μg/mL regardless of whether treatment was with vancomycin or flucloxacillin [13]. The latter finding suggests that the complex changes associated with the VISA and hVISA phenotypes have an influence on the course of infection quite apart from the efficacy of glycopeptides.

Evidence for a reduction in vancomycin efficacy against MRSA strains for which the vancomycin MIC is $\geq 2 \mu g/mL$ is accumulating; hence, the potential of clinical failure of vancomycin for treating infections caused by such strains should be considered. Risk factors for infection caused by MRSA strains with higher vancomycin MICs include exposure to vancomycin in the month prior to infection, recent hospitalisation or surgery, and bacteraemia prior to admission to an intensive care unit (ICU) [14,15]. Overcoming high vancomycin MICs by targeting higher trough levels has not been successful. In a prospective cohort study, Hidayat et al. reported that despite achieving the target trough level of at least four times the vancomycin MIC of the infecting isolate, patients in the high ($\geq 2~\mu g/mL$) vancomycin MIC group had significantly lower end-of-treatment responses (62% vs. 85%; P = 0.02) and a numerically higher mortality (24% vs. 10%; P = 0.16) compared with patients in the low (<2 µg/mL) vancomycin MIC group, with high vancomycin MIC being an independent predictor of poor outcome [16].

The global emergence of strains of *S. aureus* with reduced susceptibility to vancomycin within what is considered the susceptible range is widely acknowledged. However, there is debate about whether there has been a gradual increase in the MICs of vancomycin against *S. aureus* strains, i.e. 'MIC creep'. The phenomenon of vancomycin MIC creep, mostly in the susceptible range, was first observed in the last decade, with several independent studies reported increasing MICs in *S. aureus* strains over a variable period of time [17–20]. However, other centres found no evidence of MIC creep [21,22] or evidence of reduction in MICs over time [15]. Alós et al. demonstrated that such MIC changes were not observed in areas of low vancomycin use [23]. Kehrmann et al. suggested that the phenomenon was regional [24], whilst storage may result in reduced MICs, thus calling into

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