VISA, hetero-VISA and VRSA: The end of the vancomycin era?

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Staphylococcus aureus is a ubiquitous organism in the human population – 30% to 40% of adults are asymptomatic carriers (1). As a species, staphylococci are among the most hardy of bacteria. They survive many adverse environmental conditions including heat, desiccation and relative cold, and they tolerate high salt concentrations (2). It is therefore not surprising that *S aureus* has remained a major pathogen in humans, colonizing and infecting both hospitalized patients with reduced immune defences and healthy individuals with intact immune defences, but who have breaches to the normal skin and mucous membrane barriers. *S aureus* also illustrates the dynamic interaction between pathogenic microorganisms and antimicrobials. The isolation of *S aureus* strains that are resistant to penicillin G was reported shortly after penicillin became widely available (3). Initially a sporadic occurrence, this type of resistance, which is plasmid borne, spread rapidly through the 1950s and 1960s. By the 1970s, almost all hospital strains and a large number of community strains of *S aureus* were resistant to penicillin. The development of the semisynthetic penicillinase-resistant agents, methicillin and the isoxazoly penicillins in 1960 was followed by the report of methicillin-resistant *S aureus* (MRSA) in 1961 (4). There are several mechanisms of methicillin resistance in staphylococci, including inactivation by beta-lactamase enzymes, penicillin-binding proteins with reduced penicillin binding capacity, and the acquisition of the *mecA* gene, which encodes new penicillin-binding proteins with low affinity for beta-lactams. The latter mechanism accounts for the majority of resistance to methicillin and other beta-lactams (5).

The prevalence of MRSA in hospitalized patients was less than 5% in the early 1970s in most hospital settings worldwide, but within a decade, the prevalence had increased to as high as 40% in many hospitals in the United

States and Europe (6,7). In the past 10 to 15 years, MRSA has become increasingly recognized as a major cause of hospital-acquired infections (8). Although MRSA is not more virulent than methicillin-sensitive *Staphylococcus aureus*, there is some evidence that infections such as pneumonia, endocarditis and cellulitis with MRSA create management difficulties due to delays in recognizing the presence of a resistant strain and cross-resistance to a number of commonly used antibiotics (5). These include most beta-lactams such as penicillins, cephalosporins and carbapenems, as well as many non-beta-lactam agents. The major risk factors for MRSA colonization include prolonged hospitalization, admission to an intensive care or burn unit, previous antimicrobial drug use and contact with a known MRSA carrier. Vancomycin is the treatment of choice for serious MRSA infections.

With the increasing prevalence of MRSA worldwide and the consequent increased use of vancomycin, it was inevitable that infections with vancomycin-resistant *S aureus* (VRSA) would be reported. The first clinical isolate of *S aureus* with reduced susceptibility to vancomycin was reported from Japan in 1996 (9). The strain, known as Mu50, had a minimum inhibitory concentration (MIC) to vancomycin of 8 mg/L, which is in the intermediate range based on interpretive criteria according to the National Committee for Clinical Laboratory Standards (NCCLS) (10). Following reports of the emergence of vancomycin-intermediate *S aureus* (VISA), another type of vancomycin resistance in *S aureus* was reported from Japan in 1997 (11) and was termed hetero-VISA. These strains are susceptible to vancomycin (MIC <4 mg/L), but contain subpopulations of organisms that are capable of growing at a vancomycin concentration of >4 mg/L and have an MIC of ≥8 mg/L. In July 2002, the first documented report of clinical infection

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caused by *S aureus* that was fully resistant to vancomycin was published in the United States (12).

The nomenclature and clinical significance of vancomycin resistance in *S aureus* can be confusing. Some of this confusion arises over different breakpoints used in the literature, which can vary according to the reporting country and with the use of differing terms to describe the phenomenon of vancomycin heteroresistance in subpopulations of *S aureus*. In addition, commonly used laboratory techniques for determining antibiotic susceptibility to vancomycin have proved to be less than optimal for detecting VISA and hetero-VISA. Most laboratories in Canada follow the guidelines set out by the NCCLS (10), in which staphylococci with an MIC of ≤ 4 mg/L to vancomycin are considered to be susceptible, those with an MIC of 8 to 16 mg/L are intermediate and those strains with an MIC of ≥ 32 mg/L are resistant. Disk diffusion testing has been found to misclassify VISA as fully susceptible (13), and automated testing methods such as MicroScan (Dade Behring Inc, USA) and Vitek (BioMérieux Inc, USA) have failed to identify VISA strains (13,14). At present, MIC determinations using broth dilution, agar dilution or E-test are considered to be the best methods for detecting reduced susceptibility to vancomycin (14,15). The Centers for Disease Control and Prevention (16,17) have published recommendations to guide laboratories in the susceptibility testing of *S aureus* isolates to detect increased MICs to vancomycin. Although a VISA strain would be expected to exhibit an MIC of ≥ 8 mg/L, the hetero-VISA strain has generally required formal population analysis using the serial passage of screened isolates of *S aureus* on selective agar containing increasing concentrations of vancomycin for detection (18). This type of testing is beyond the scope of most clinical laboratories.

VISA clinical isolates have been reported from Japan, the United States (Michigan, New Jersey, New York and Illinois), the United Kingdom, France and Hong Kong (9,19-25), and clinical failures to vancomycin treatment have been well documented with these isolates. Hetero-VISA strains have been reported from Japan, Hong Kong, Spain, Italy, Germany and Korea (11,25-29). The identification of hetero-VISA has suggested that some *S aureus* strains regarded as 'susceptible' by MIC testing may represent a continuum between VISA isolates and truly susceptible populations of *S aureus*. The prevalence of hetero-VISA varies and appears to be dependent on the population and geographical area. In the study from Spain (26), in which only MRSA isolates from surgical site infections in orthopedic patients were screened, 65% of the strains had subpopulations with elevated MICs to vancomycin. At present, the clinical significance of hetero-VISA is not understood fully. One retrospective study suggested that patients who were infected with hetero-resistant strains causing bacteremia had a higher mortality rate than patients who were infected with fully sensitive strains (30), and another study suggested a higher failure rate with vancomycin in patients with

surgical site infections (26). However, other studies have not found any relationship between hetero-VISA and treatment failure with vancomycin (29).

The relationship between hetero-VISA and VISA is interesting, however, and several lines of evidence suggest that hetero-VISA strains give rise to VISA after prolonged exposure to glycopeptides. Clonal relationships have been reported between hetero-VISA and VISA strains isolated from the same hospital or region (31,32), and between a vancomycin-susceptible MRSA and a VISA strain isolated from the same patient (33,34). In vitro, the level of vancomycin resistance of hetero-VISA has been reported to be increased by exposure to higher concentrations of vancomycin in a stepwise fashion (34).

The mechanism of resistance in hetero-VISA and VISA involves a complex reorganization of cell wall metabolism, leading to a grossly thickened cell wall with reduced glycopeptide cross-linking (33,34). Before the identification of this finding in clinical isolates of VISA, laboratory-induced strains of VISA were noted to have thicker cell walls than the parent strains (35). It has been proposed that the thickened cell walls may trap and sequester vancomycin and, thus, limit its effect by preventing penetration to its site of action (36,37).

The mechanism of resistance described for the first clinical isolate of VRSA reported in the United States (12) was related to the presence of the *vanA* vancomycin resistance gene, which has been described in enterococci. The MIC for vancomycin for this strain was >128 mg/L by the broth microdilution method. The presence of the *vanA* gene in this isolate, the presence of a vancomycin-resistant *Enterococcus fecalis* in the wound of the patient and the previously demonstrated in vitro conjugative transfer of the *vanA* gene from enterococci to *S aureus* (38) suggest that this latter phenomenon occurred in the clinical setting.

While no isolates of *S aureus* with intermediate or complete resistance to vancomycin have been described in Canada, there is a need for continued vigilance within clinical microbiology laboratories. The appearance of hetero-VISA and VISA appears to be more common given the number of reports in the literature. It is interesting to note that, despite the coexistence of MRSA and vancomycin-resistant enterococci in the clinical setting for more than 14 years in the United States, VRSA has not appeared until now. Although the event may be rare, once a patient becomes colonized, the major concerns are the horizontal transfer between patients and the establishment of an endemic focus. Unfortunately, little is known about the epidemiology or risks for the horizontal transfer of hetero-VISA and VISA. This is only the beginning of the era of vancomycin resistance in *S aureus* and other staphylococcal species. Much work must be done to fully elucidate the mechanisms of resistance, the risk factors for their occurrence, the optimal management of patients who are infected with these organisms and, ultimately, how best to prevent them from spreading.

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