CANADIAN ANTIMICROBIAL RESISTANCE ALLIANCE

## VANCOMYCIN RESISTANT STAPHYLOCOCCUS AUREUS (VRSA)

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For many years vancomycin has been considered the drug of choice for the treatment of Staphylococcus aureus infections due to strains that had become resistant to methicillin [so-called Methicillin Resistant Staphylococcus aureus (MRSA)]. However, in July 2002, things changed when the Centers for Disease Control (CDC) in the USA published the first documented report of Staphylococcus aureus that was resistant to vancomycin as well as being resistant to methicillin. The infection occurred in a diabetic patient with chronic kidney (renal) failure who was undergoing peritoneal dialysis in a hospital in Michigan. Approximately 5 years earlier, the Japanese had reported the first strain of S. aureus with reduced (or intermediate) susceptibility to vancomycin followed by 2 additional cases from the USA. These earlier isolates were termed Vancomycin Intermediate Staphylococcus aureus (VISA). Although additional cases have been reported from other countries, to date, no cases of either VISA or VRSA have been identified in Canada.

The definitions of VRSA and VISA are based on the results of laboratory testing which determine the minimum concentration of vancomycin that is required to inhibit the growth of *S. aureus* in a "test tube". It should be noted that these definitions are not universal and some countries lump all strains of *S. aureus* that require increased concentrations of vancomycin to inhibit their growth into a single VRSA category. Regardless of the specific categorization of these isolates, the potential clinical impact of these strains on the management of patients is enormous.

The mechanisms of resistance that have been identified for VISA and VRSA strains are quite different and are not fully understood. For VISA strains, the proposed mechanism resulting in reduced susceptibility to vancomycin is believed to be a thickening of the bacterial cell wall such that vancomycin is trapped within the bacterial cell wall and is thus unable to reach its target on the surface of the bacterial cytoplasmic membrane. The VRSA strain that was isolated from the patient in Michigan as well as a second isolate from a patient in Pennsylvania contained the vanA gene which codes for an altered target such that the binding of vancomycin to the target is significantly reduced and thus it cannot carry out its normal function of inhibiting bacterial cell wall synthesis. The source of the vanA gene isolated in VRSA appears to have come from co-infection with vancomycin resistant enterococcus (VRE).

The number of cases of VISA and VRSA reported thus far has remained relatively small and thus the epidemiology and risk factors associated with infection with these organisms is not completely known. However, there is evidence that prior exposure to vancomycin, particularly repeated or prolonged courses, in patients who are infected or colonized with MRSA are at highest risk for developing infection with *S. aureus* with reduced susceptibility to vancomycin. For patients infected with VISA strains, in-hospital mortality appears to be significantly increased compared to patients who are infected with vancomycin susceptible *S. aureus*.

Because of the variable antibiotic susceptibility patterns for VISA strains, there are no uniform recommendations for treatment of infections due to this organism. Agents such as quinupristin-dalfopristin, linezolid, tetracycline, trimethoprim-sulfamethoxazole (TMP-SMX), tigecycline and daptomycin, have all been used alone or in combination with other agents for the treatment of some VISA infections. The 2 reported VRSA strains in the USA were found to be susceptible to quinupristin-dalfopristin, linezolid, TMP-SMX but resistant to tetracycline. At the moment, treatment of VISA or VRSA strains should be based on the results of laboratory susceptibility testing.

The future of VISA and VRSA strains is not clear and much research is needed to help further understand all aspects of these organisms including their epidemiology, microbiology, clinical and infection control implications and optimal treatment. As well, in addition to VISA and VRSA strains, there appear to be strains of *S. aureus* that are referred to as "heteroresistant." These strains appear to be susceptible to vancomycin based on standard laboratory testing, but contain subpopulations of *S. aureus* that have intermediate susceptibility to vancomycin. The clinical significance of these strains requires further investigation.

## **Selected References:**

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