Staphylococcus aureus; will vancomycin resistant strains become common in the future?

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Staphylococcus aureus (S. aureus) is an aggressive pathogen that is a common cause of infections both in the community and in hospitals. Before the advent of antibiotics S. aureus bacteremia was associated with an 80% mortality and the disease often occurred in young adults. The advent of penicillin marked a major breakthrough in the treatment of serious S. aureus infections. However, many of these benefits were lost within 10 to 15 years of the introduction of penicillin because of the widespread resistance that developed along with widespread dissemination of these resistant bacteria.

In the late 1950’s during an influenza outbreak there were many people who died of what was again untreatable S. aureus infections. We were however fortunate in the late 50s and early 60s because new antibiotics were developed to overcome this problem. Vancomycin was developed and its release was closely followed by beta-lactamase stable penicillins (such as methicillin and later cloxacillin). Cephalosporins which have activity against S. aureus also subsequently became available.

In the 1960’s and 70’s methicillin resistant S. aureus (MRSA) developed and became widespread in hospitals around the world. These strains could no longer be efficiently killed by any beta-lactam antibiotic (methicillin, flucloxacillin or cephalosporins). Vancomycin remained the only predictable active antibiotic against all strains of S. aureus and MRSA in particular. Until recently there have been no strains of S. aureus that would not respond to vancomycin, providing vancomycin could reach the site of infection. The recent discovery of a vancomycin resistant strain of S. aureus (initially abbreviated as VRSA) in Japan has been to many microbiologists a nightmare scenario. It is of concern that these resistant strains have already been found in other countries including the United States of America and France.

These strains do not appear to have developed from just a single clone of S. aureus. They are generally in the intermediate level of resistance to vancomycin with moderately raised minimal inhibitory concentrations (MICs). They have previously been described as ‘vancomycin intermediate resistant S. aureus’ (VISA). However, they are frequently also resistant to the other glycopeptide used in clinical practice (teicoplanin) and are therefore more accurately described as GISA (with the G referring to glycopeptides). They appear to have developed from strains of MRSA. Many of the clinical and laboratory difficulties in treating and recognising this new and emerging infection are discussed by Paterson in the accompanying article. It is of interest that there were similar difficulties in the laboratory recognition of strains of MRSA when they were initially discovered.

The concern regarding the development of VRSA was particularly worrying because of the now widespread occurrence of vancomycin resistant strains of enterococci (VRE). Enterococci are generally much less virulent than S. aureus, however VRE bacteraemia is associated with a higher mortality when compared to strains that remain antibiotic sensitive. In the laboratory, the complex genome coding for vancomycin resistance has been transferred to S. aureus. VRE is more likely to occur in long term hospital patients and these patients are also frequently colonised with MRSA. Because vancomycin remains one of the few (and in many cases the only) antibiotic to treat MRSA, there is concern that the genetic material encoding for vancomycin resistance in enterococci could transfer to clinical isolates with MRSA. To date this does not appear to have occurred (or at least been described in the literature).

What was surprising about the Japanese and the American isolates is that the mechanism of resistance appears to be different from the vancomycin resistance in VRE. In some strains of S. aureus it involves a markedly altered and thicker cell wall as well as changes in penicillin binding proteins. This again however highlights one of the problems with bacteria and antibiotic resistance. We frequently do not have the ability to accurately predict what will happen in the future. Microbes have the ability to come up with unexpected and novel mechanisms of resistance.

Vancomycin may be needed more frequently to treat community-acquired infections. We are recently seeing a new variety of MRSA that are now circulating in the community (cMRSA), and not infrequently causing serious infections. They are particularly common in some areas in New Zealand, but also found in Australia and the United States of America. Fortunately most strains of cMRSA are not multi-resistant and there remain some therapeutic options available besides vancomycin. However, if we look at what has occurred with MRSA in the past in hospitals, it is almost inevitable with time that these cMRSA strains will become resistant to currently available agents. Some new agents such as ‘Synercid’ are being developed but even in these new agents there has already been resistance encountered in enterococci (that may partially be related to the use of a similar agent, virginiamycin, in animals as growth promoters).

The other concern, besides the development of having strains resistant to all available antibiotics (and those in the pipeline), is the ability of these strains to disseminate. Strains of MRSA that show heterogeneous resistance to vancomycin have already spread within some Japanese hospitals. In the teaching hospital where the GISA strain was first isolated 20% of MRSA strains show heterogeneous resistance to vancomycin. In seven other teaching hospitals the rate was 9.3% and in non university
hospitals it was 1.3%. If the numbers have increased so rapidly in Japan, and are now being found elsewhere in the world, it would appear inevitable over the next five to ten years that they will approach levels, in particularly hospital situations, that we are seeing with MRSA (between 20-50% in many institutions). In addition to GISA strains, this resistance can also be seen in some MRSA strains which can be heteroresistant.

The question is what can Australia do about this. Unfortunately once these strains have developed there is no way of putting the ‘genie’ back into the bottle. We need to slow down the spread and amplification of these strains as much as possible (by good infection control, conservative measures, prudent use of antibiotics, and good hygiene). Hopefully then, in the next few years new antibiotics will be developed that will be active against GISA (or fully vancomycin resistant strains when they inevitably occur). We should not use antibiotics when they are not needed. When we do use antibiotics we should use as narrow a spectrum agent as possible. This means in particular, avoiding using agents such as vancomycin unless it is essential.

Antibiotic resistance is an inevitable consequence of antibiotic use, whether they are used appropriately or inappropriately. However, the rate of rise of antibiotic resistance, and amplification of these bacteria, can be modified by our behaviour through improved hygiene, infection control and the most appropriate use of antibiotics.

References
2. Collignon P et al. Antibiotic resistance: is it leading to the re-emergence of many infections from the past? Australian society for Microbiology, Melbourne. Recent advances in Microbiology. Edited by Val Asche p 203-256.

Further reading

Victorian measles outbreak
In the face of a continuing rise of reported measles cases among young adults in Victoria, the Communicable Diseases Network of Australia New Zealand (CDNANZ) have called on all Australians aged 18 to 30 to check their vaccination status.

The measles outbreak was first reported in the western suburbs of Victoria several weeks ago and has now spread to involve young adults in the northern and eastern suburbs and border areas.

Everyone should be protected against measles and other vaccine-preventable diseases by vaccination. The recent successful primary schools campaign appears to be protecting children in that age group.

Statistics at 23 March 1999
• 41 cases of measles have been reported to Victorian Health authorities.
• the index case was a young adult who had returned from Bali.
• 90% of cases are between 17 and 27 years of age.
• 2 cases are in the 30 to 34 age group.
• 1 case is a 10 months old child - below the recommended age for routine immunisation at 12 months of age.
• 1 case is an unimmunised 8 year old boy.
• 40% of cases have been admitted to hospital.