A resistant culture - ‘superbugs’ in Australian hospitals

Introduction

Antimicrobial resistance is not new in Australian hospitals. In 1946, shortly after penicillin became available for treatment of civilians, a penicillin resistant Staphylococcus aureus strain caused ~50% of staphylococcal surgical wound infections at the Royal Prince Alfred Hospital (RPAH), in Sydney. During the 1950s, another virulent penicillin resistant S. aureus strain (phage type 80/81) emerged in neonatal units in Sydney and spread to other hospitals in Australia and overseas, to the families of affected infants and to the general community, causing serious soft tissue infections, osteomyelitis, pneumonia and septicaemia. Methicillin was introduced in Australia in 1961 and methicillin resistant S. aureus (MRSA) was first identified at RPAH in 1965. By the 1970s, MRSA was endemic in many major hospitals in the eastern states but largely excluded from Western Australian hospitals by a systematic ‘search and destroy policy’. Enhanced, statewide surveillance and control policies recently implemented in Queensland and South Australia, have led to a reduction in MRSA rates. Since 1994, vancomycin-resistant enterococci (VRE) have caused intermittent outbreaks and have become endemic in some clinical units in Australia. Multiresistant gram-negative infections, due to the spread of novel resistance genes into potentially pathogenic Enterobacteriaceae and other opportunistic pathogens, can cause serious and occasionally untreatable sepsis.

Epidemiological data on healthcare associated infections (HCAI) and multiresistant organisms (MRO) in Australia are limited. There are no national surveillance data and there are significant differences between states and territories, and in some jurisdictions between hospitals, in screening and control policies. Despite a strong consensus among infection control experts that a national approach to surveillance control is needed, there has been limited administrative support and resource allocation in some jurisdictions. However, there are encouraging signs that the disease burden and public health importance of antibiotic resistance and HCAI are at last being recognised by health administrators and bureaucrats. For example, the New South Wales Department of Health has recently published recommendations for MRO control and allocated funds to implement them and the Australian Commission on Safety and Quality in Healthcare has nominated healthcare acquired infections as one of nine priority patient safety programs.

MRSA

There have been wide variations in MRSA rates in different Australian states. In 1967, 6% of S. aureus isolates at RPAH were MRSA; by 1970 this increased to 73%, after a virulent strain was introduced from New Caledonia. In Victoria, fewer than 2% of S. aureus isolates were MRSA before 1975 but by 1979 this had risen to 20–40% in thirty-one metropolitan hospitals.

Among 19,000 clinical S. aureus isolates collected between 1989 and 1999 from twenty-one Australian teaching hospitals, 20% were MRSA. In 1989 proportions varied from 20–40% in Brisbane, Melbourne and Sydney, to <5% in Adelaide and Perth. By 1999 rates had increased overall, but the greatest increase was from <5%–~35% in Adelaide. Most isolates (>95%) were multiresistant MRSA except in Perth, where most were non-multiresistant, reflecting mainly community acquired MRSA on a background of infrequent hospital acquisition.

A review of S. aureus bacteraemias in seventeen Australian hospitals between 1999 and 2002, showed that 51% were hospital acquired and of these, 40% were due to MRSA – compared with 12% of community onset episodes. Based on these data, it was estimated that ~1500 MRSA bloodstream infections occur each year in Australia. Although bloodstream infections represent only a small proportion of significant MRSA infections, they provide an objective measure of MRSA disease burden. Ratios of MRSA to methicillin susceptible S. aureus (MSSA) and community acquired to HCA bacteraemias reflect the quality of hospital infection control and antibiotic prescribing and are useful surveillance measures. The most recent data on HCA MRSA bacteraemias in Australia are limited. In Western Australia and many European countries and falling rates following the introduction of improved surveillance and control programs in some Australian states, indicate that this is possible.
The majority of hospital-associated MRSA isolates in the eastern states of Australia are multiresistant epidemic MRSA Aus-2/3 strains, which belong to one of the most widely distributed multiresistant hospital clones worldwide. A significant and probably increasing minority belong to the highly transmissible EMRSA-15 strain, which emerged and spread widely in the United Kingdom during the 1990s and was first identified in Australia in 2001. The main characteristics of these two MRSA strains are shown in Table 2.

**Vancomycin intermediate and resistant S. aureus**

Despite forty years of extensive and sometimes inappropriate medical use of vancomycin and the veterinary use of another glycopeptide (avoparcin), glycopeptide resistance in MRSA was not identified until the 1990s. *S. aureus* isolates with reduced susceptibility to vancomycin (VISA) were first reported in Japan in 1997 and in Australia in 2001. VISA strains have since been reported in many countries. Definitions vary, but generally they are defined as *S. aureus* with vancomycin minimum inhibitory concentrations (MIC) of 4–16 mg/L. Some strains with vancomycin MIC <4 mg/L contain a resistant subpopulation (heterogeneous (h)VISA). The prevalence and clinical significance of VISA in Australia (and elsewhere) are uncertain because of difficulty identifying them. Conventional susceptibility testing methods are relatively insensitive. High inoculum E-tests are more reliable but usually performed only on the basis of clinical suspicion. Confirmation requires ‘population analysis profiling’, which is time-consuming and not widely available.

Development of VISA does not involve major genetic change. It is an adaptive response to sublethal vancomycin exposure causing thickening of the staphylococcal cell wall with increased production and turnover of D-alanine-D-alanine residues (which bind glycopeptides) in the peptidoglycan layer, involving several genes. Vancomycin MIC can increase during treatment, especially in patients with high MRSA bacterial loads (such as endocarditis) or suboptimal vancomycin levels, leading to persistent bacteraemia and treatment failure.

Several separate incidents of transmission of vanA (encoding high level glycopeptide resistance) from *Enterococcus faecium* to *S. aureus* – causing vancomycin resistance (VRSA) – have been described since 2002 in the USA. So far, VRSA has not occurred in Australia, but the risk will remain while high rates of MRSA (and VRE – see below) colonisation and vancomycin use continue in some Australian hospitals.

**VRE**

Medically significant VRE were first described in England and Europe in 1988. There was strong circumstantial evidence that the emergence of VRE in humans was associated with widespread use of avoparcin for growth promotion and prophylaxis in animals. This was supported by the fact that VRE could be isolated quite commonly, from farm animals and healthy people in Europe, although hospital outbreaks were relatively uncommon. Within a few years, VRE also emerged in the USA. Vancomycin was much more widely used in hospitals in the USA than in Europe, but avoparcin had not been used in animals. This was reflected by the fact that in the USA VRE was not found in healthy people or animals, but it spread rapidly among hospitalised patients. Recently, VRE represented 14–25% of all clinically significant enterococci and contributed significantly to excess mortality among infected patients.

In Europe and the USA, VRE are mainly *Enterococcus faecium*, in which high level vancomycin and teicoplanin resistance are mediated by *vanA*. Most hospital outbreaks of VRE are caused by a single virulent genotype, with a variant enterococcal surface protein (esp) gene, which differs from those found in animals and healthy people in Europe.

In Australia, VRE was first isolated in 1994 from a liver transplant patient at the Austin Hospital, Melbourne, and there have been numerous reports of ‘outbreaks’ (and many others not reported) since then. In Australia, too, most VRE are *E. faecium* but, in contrast to Europe and the USA, most carry *vanB* and are typically susceptible to teicoplanin with low level vancomycin resistance, although MICs vary widely. Avoparcin was used in animals in Australia until ~2000, but limited data suggest that neither *vanA* nor *vanB* VRE were common in animals. The origin of VRE in Australia is unknown, but *vanB* can be found in gram-positive anaerobes, especially *Clostridium* spp. in the normal faecal flora, which are a potential reservoir of transmission to enterococci.

Several VRE outbreaks in Australian hospitals have been reported and successfully controlled, albeit at considerable cost. There are no national surveillance data on the prevalence of VRE. Outbreaks (mainly of colonisation) occur, particularly in renal dialysis, transplant, haematology and intensive care units, where there is widespread and often repeated use of antibiotics, such as third generation cephalosporins, which select out enterococci, and vancomycin, which select for VRE. Risk factors for VRE transmission among critically or chronically ill patients, especially if immuno-suppressed (and prone to diarrhoea), include: inadequate hand hygiene (by ambulatory patients and visitors as well as busy staff); environmental contamination and too few isolation rooms. Screening for VRE carriage is complicated by difficulties in detection of *vanB* strains, which often have low level resistance. Moreover, hospitals and units at risk from VRE are also those most likely to have high levels of MRSA endemicity and isolation of the VRE colonised patient may compromise MRSA control because of competition for limited resources.

**Multiresistant gram-negative bacteria**

Antibiotic resistance in gram-negative bacteria is more complex than in gram-positive bacteria. Their resistance genes are more varied, more readily transmissible and more difficult to define and identify. The bacterial species and resistance genes involved at different times and places in Australia in recent years include: various Enterobacteriaceae containing extended spectrum betalactamases (ESBL) including *E. coli* and *Klebsiella pneumoniae* containing *bla*-*OXA* and *CTX-M*; carbapenem resistant *Acinetobacter baumannii* carrying the serine protease gene *bla*-OXA-23; and various *Enterobacteriaceae* and *Pseudomonas aeruginosa* carrying the metalloenzyme *bla*-IMP-1.
The mechanisms of transmission and expression of these genes are complex. Screening of high-risk patients by PCR, for relevant resistance genes – rather than phenotypically resistant species – is a logical approach, but interpretation is complicated by bacterial host-dependent variation in expression and possible changes in the prevalent resistance genes. Moreover, the predictive values of this approach have not yet been evaluated. On the other hand, there is increasing evidence that unless appropriate control measures are instituted, resistance genes can become established and increasingly difficult to manage.

Conclusion
In some Australian hospitals, the rates of preventable, serious and potentially fatal HCAI due to MROs are unacceptably high. The urgent need to address this is at last being recognised nationally, although in some states (e.g. New South Wales and Victoria) where the problems are greatest and have been entrenched the longest, it will not be easy to achieve adequate control. The most important prerequisite is a major culture change with acceptance of responsibility and commitment of resources by health administrators and senior clinicians, and personal accountability by all healthcare workers for best infection control practice (including hand hygiene and antibiotic prescribing). Among other requirements are consistent, continuous surveillance with rapid feedback to clinicians and appropriate responses; more sensitive, faster screening and strain typing methods, and adequate staffing and better physical resources (such as single rooms) in hospitals. The cost of these measures will be more than repaid in reduced morbidity and mortality and shorter hospital stays.

References

Table 1. Estimated recent annual rates of healthcare-associated bacteraemia

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Population x 10^5 b</th>
<th>Cases per annum c</th>
<th>Incidence/100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Capital Territory</td>
<td>3.3</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>New South Wales</td>
<td>67.7</td>
<td>500</td>
<td>7.4</td>
</tr>
<tr>
<td>Northern Territory (Darwin)</td>
<td>1.2</td>
<td>16</td>
<td>13.3</td>
</tr>
<tr>
<td>Queensland</td>
<td>39.6</td>
<td>133</td>
<td>3.4</td>
</tr>
<tr>
<td>South Australia</td>
<td>15.4</td>
<td>37</td>
<td>2.4</td>
</tr>
<tr>
<td>Tasmania</td>
<td>4.7</td>
<td>3</td>
<td>0.64</td>
</tr>
<tr>
<td>Victoria</td>
<td>50.2</td>
<td>300</td>
<td>6.0</td>
</tr>
<tr>
<td>Western Australia</td>
<td>20.1</td>
<td>22</td>
<td>1.1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,040</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
a. Data are based on 1–5 year periods between 2000 and 2006, using different surveillance methods.
b. Populations (rounded to nearest 100,000) from Australian Bureau of Statistics.
c. Data for New South Wales and Victoria are approximate and probably underestimates, they are averaged over several years.


**Table 2. Characteristics of the major hospital MRSA strains in Australia.**

<table>
<thead>
<tr>
<th>“Hospital” MRSA strains:</th>
<th>AU5-2/3 EMRSAb</th>
<th>UK EMRSA-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequence type (ST)</td>
<td>239</td>
<td>22</td>
</tr>
<tr>
<td>Clonal complex (CC)</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>SCCmec type</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>Urease</td>
<td>+ve</td>
<td>-ve</td>
</tr>
<tr>
<td>Antibiogram (2003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistant Susceptible</td>
<td>&gt;97% to ery, gent, tet, cipro, trim&lt;sup&gt;c&lt;/sup&gt;</td>
<td>100% to cipro; 69% to ery&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>&gt;95% to fus, rif, mupc</td>
<td>100% to gent, tet, trim, fus, rif, mupc</td>
</tr>
<tr>
<td>% of all MRSA (2003)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Aus-2, 43%/Aus-3, 22% = 65%</td>
<td>9%</td>
</tr>
<tr>
<td>% of “hospital” MRSA, (2003)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Aus-2, 58%/Aus-3, 29% = 87%</td>
<td>12%</td>
</tr>
</tbody>
</table>

**Notes:**

a. Based on report of Australian Group on Antibiotic Resistance (AGAR) \textit{Staphylococcus aureus} Program, 2003 (AGAR 2003). —100 consecutive isolates from individual patients attending 25 hospitals around Australia — total 2,184 - were tested. Overall ~25% of isolates were non-multiresistant community MRSA strains. Of the 75% 'hospital’ or epidemic MRSA strains <1% belonged to other clones.

b. Aus 2 and Aus 3 strains are distinguished on the basis of their susceptibility (Aus 2) or resistant (Aus 3) to mercuric compounds.
c. Isolates were tested for susceptibility to 8 antibiotics: ery = erythromycin, gent = gentamicin; tet = tetracycline; cipro = ciprofloxacin; trim = trimethoprim; mup = mupirocin.