

Multiple drug resistance in *Staphylococcus aureus*

A time-bomb for Jamaica and the region

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Staphylococcus aureus (staph) is a bacterium commonly found as a commensal on the skin and in the nose of up to 70 per cent of healthy individuals (Wertheim et al., 2005). While staph does not cause any harm most of the time, when it does, serious infections can be the result, including bacteremia or sepsis, skin and soft-tissue infections, pneumonia, endocarditis or osteomyelitis.

Antibiotics are naturally occurring, semi-synthetic compounds that have antimicrobial activity such as bactericidal or bacteriostatic effects and are used for the prevention and treatment of clinical infections in both human and veterinary medicine. While antimicrobial resistance is an inevitable evolutionary response to antimicrobial use, it has become a major threat to public health as health officials try to contain drug resistance, which particularly complicates the therapeutics for control and limits what is available for emerging infections.

For many years, we have been faced with the emergence and spread of microorganisms resistant to one or more antimicrobial agents commonly used in the treatment of infections. In some cases, pathogens have become resistant to all anti-infectious drugs – for example, extreme- and multi-drug resistant *Mycobacterium tuberculosis*, leading to therapeutic failure (Pinto and Menzies, 2011). While most multiple drug resistant (MDR) pathogens were traditionally associated with hospital-based (nosocomial) infections, most notably methicillin-resistant *Staphylococcus* species (MRSA and coagulase-negative staphylococci), penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci (VRE) and multi-resistant Gram-negative bacilli – such as *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa* – many are being isolated from community sources. Nosocomial infections affect a significant proportion of patients in intensive care units (ICUs) and are associated with substantial morbidity and mortality, and increased costs. Furthermore, the prevalence of antibiotic-resistant pathogens isolated in the ICU is usually significantly higher than in other hospital wards. This has precipitated a plethora of strategies to contain these organisms, while the scientific community struggles to keep pace with the need to devise new combinations of drugs.

In Jamaica, health services are delivered through four semi-autonomous regional health authorities (RHA) that have direct management responsibility within a geographically defined region. North East RHA comprises the parishes of St Ann, St Mary and Portland; South East RHA includes Kingston and St Andrew, St Catherine and St Thomas; Southern RHA comprises St Elizabeth, Manchester and Clarendon; and Western RHA manages the parishes of Westmoreland, Hanover, St James and Trelawny. Locally,

the traditional approach has been to assess the prevalence of multiple drug resistance among important nosocomial pathogens, primarily in the intensive care units. However, in more recent times, attention has been given to investigation of molecular resistance determinants, such as the presence of transmissible plasmids, for example *qnr* plasmids in *E. coli*, and mobile genetic elements, for example the staphylococcal cassette chromosome *mec* (SCC*mec*) elements in community- and hospital-acquired MRSA, and integrons in *E. coli*.

This article highlights the local situation in Jamaica in relation to multiple drug resistance in MRSA and implications for clinical practice. The same issues may apply to many other bacterial and viral pathogens encountered in Jamaica, and should be envisioned collectively as a ticking time bomb, which requires immediate action.

Evolution of MRSA in Jamaica

Staph is naturally susceptible to many classes of antimicrobials but has the ability to develop multiple resistances. For example, penicillin resistance due to the production of plasmid-mediated penicillinase appeared in staph soon after the introduction of penicillin, and had affected 85 per cent of both hospital and community isolates by the late 1970s. In the 1950s and early 1960s, hospital outbreaks with strains resistant to penicillin, tetracycline, erythromycin and chloramphenicol became common, but these disappeared after the introduction of methicillin and other penicillins resistant to breakdown by staphylococcal penicillinase.

Gentamicin resistance became common in the 1970s, and in the 1980s methicillin- and multiple-resistance emerged throughout the world. In both the USA and Europe, at least 26–50 per cent of hospital isolates of staph are MRSA (NNIS, 2002); although in the Netherlands and Scandinavia MRSA rates are less than one per cent (EARSS, 2001).

Many strains of MRSA remain reliably susceptible only to the glycopeptides vancomycin and teicoplanin, and vancomycin is the drug of choice for serious infection. Unfortunately, several types of glycopeptide resistance have emerged in MRSA in recent years. Some isolates show glycopeptide tolerance; that is, they are inhibited by normal concentrations of glycopeptides but are not killed. Tolerance has been associated with treatment failures, but its exact clinical significance is unclear. Occasional strains of staph with chromosomally encoded low-level or 'intermediate' resistance to vancomycin have appeared in Japan, North America and Europe



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(Liu and Chambers, 2004) associated with treatment failures and designated 'vancomycin-intermediate' or 'glycopeptide-intermediate' staph (VISA or GISA). Up to the end of 2006, seven isolates of VRSA had been reported from the USA with high-level glycopeptide resistance of the VanA type, probably derived from vancomycin-resistant enterococci (CDC, 2004). Although still exceptionally rare, these dangerously resistant organisms may become more frequent in the future.

In Jamaica, MRSA was first recognised in 1991 at the University Hospital of the West Indies. Previous work (Bodonaik et al., 1984) reported that 82 per cent of isolates from outpatients and 84 per cent of those from inpatients at the University Hospital of the West Indies (UHWI) were resistant to penicillin. The UHWI is a 600-bed multi-disciplinary teaching hospital, which serves the metropolitan area of Kingston and St Andrew. In that study, no methicillin resistance was found. However, by 1991 the incidence was 5.1 per cent and by 1997 this had increased to 9.3 per cent. A study in 2003 in Mandeville, situated about 124 km from the Kingston and St Andrew metropolis, noted that 87 per cent of the staph isolates were resistant to penicillin and 24 per cent were methicillin-resistant (Brown and Ngeno, 2007). Interestingly, all of these MRSA isolates were from community sources. Historically, methicillin-resistant isolates are also resistant to all beta-lactam agents, including the cephalosporins and carbapenems. Continuing active surveillance noted a fall in the incidence of MRSA at the UHWI to

four per cent in 2004, with an increase to seven per cent during 2008 (Nicholson et al., 2010).

MRSA is a major cause of hospital-acquired infections and has also recently established itself as a significant community-acquired pathogen. Hospital-acquired (HA-) MRSA are generally multidrug resistant and contain types I, II or III of SCC*mec* (for staphylococcal cassette chromosome *mec*, the mobile genetic element encoding methicillin resistance; Ito et al., 2001). In contrast, community-acquired (CA-) MRSA differs from HA-MRSA in that it does not generally belong to the major clonal groups of epidemic MRSA, is susceptible to most non-beta-lactam antibiotics, contains SCC*mec* types IV or V, and frequently carries genes responsible for the production of Panton-Valentine leukocidin (PVL; Fey et al., 2003; Liassine et al., 2004; Naimi et al., 2003).

CA-MRSA, as a cause of infection in the hospital setting, was first identified at the UHWI in 1997; then it accounted for 12.1 per cent of MRSA-associated infections. This increased to 25 per cent in 2004, 28 per cent in 2006 and 45 per cent in 2008 (unpublished data) – a worrying trend as significant infection control measures have been put in place since 2004. In addition, most of the affected patients were surgical and medical patients, with significant association with the ICU and surgical wards. Other local surveillance has also noted an increase in the number of CA-MRSA infections.

A recent study by Chroboczek et al. (2013) revealed that the distribution of the major MRSA clones in the French (Guadeloupe and Martinique) and non-French West Indies (Jamaica, and Trinidad and Tobago) is different, and the clones most closely resemble those found in the home countries of the travellers who visit the islands most frequently. The authors suggested that the local distribution might be affected by tourist migration, which is specific to each island.

MRSA, MSSA and clinical outcome

There has been much debate over whether MRSA infections have a worse outcome than those caused by methicillin-sensitive strains (MSSA). However, this issue has been resolved by a meta-analysis by Cosgrove and colleagues (2003), who reviewed studies comparing MRSA and MSSA bacteremia published between 1980 and 2000. Nearly 78 per cent of these studies failed to show an effect of MRSA on mortality, probably because individual studies lacked statistical power. However, the pooled results showed a significant excess mortality associated with MRSA bacteremia (odds ratio 1.93; 95 per cent confidence interval, 1.54–2.42). The authors thought that since the mean mortality rate for MSSA bacteremia was 23 per cent, the odds ratios might have overestimated the effect. They therefore calculated a pooled relative risk of 1.42, which they thought better reflected the magnitude of the effect. The increased mortality remained after adjusting for nosocomial infection, the presence of an outbreak, central venous catheterisation and endocarditis. The effect of MRSA on mortality was lower in patients with central venous line infections, perhaps because these patients can be readily treated by removal of the focus of infection.

Similar results were found when surgical site infections with MRSA and MSSA were compared (Engemann et al., 2003). Those with an MRSA infection had a significantly greater 90-day mortality rate, a greater length of hospitalisation and significantly increased hospital charges compared with patients with MSSA surgical site infection. In Jamaica, one-third of patients colonised by MRSA develop infection and there is an increased risk of death from MRSA (odds ratio 1.93). In addition, there is significant morbidity, particularly due to increased incidence of MRSA-associated bacteremia and shock. Costs associated with MRSA hospitalisation are significant, with drugs costing between US\$325 to \$574 and patients needing 14 to 36 bed days. In addition, because these patients become a source of infection, there might be other persons to treat. For the patient, hospitalisation fees per day can range from JM\$3024 to \$12,835, and while most of these costs can be recouped because of insurance, the emotional toll on the patient is often priceless. Possible reasons why MRSA is associated with poor outcome include enhanced virulence, decreased effectiveness of vancomycin, which is widely used to treat MRSA, and delay in implementation of appropriate therapy. However, there is no evidence so far that MRSA is any more or less virulent than MSSA, a conclusion we made in a recent study of MRSA and MSSA in Jamaica looking at 35 virulence genes. This indicates that virulence of MRSA per se is not responsible for the increased cost associated with higher mortality, longer hospital stays and length and severity of infection as suggested by some authors (Shurland et al., 2007; Cosgrove, 2006).

We also noted that multiple drug resistance was more associated with MRSA when compared with MSSA. Teicoplanin (3.8 per cent),

chloramphenicol (15.4 per cent) and mupirocin (18.3 per cent) were the antibiotics with the lowest resistance rates and therefore the antibiotics most effective against MRSA in Jamaica (unpublished results). Teicoplanin, like vancomycin, belongs to the glycopeptide group of antibiotics currently used as a drug of last resort for the treatment of staph infections. However, the glycopeptides are relatively poor anti-staphylococcal antibiotics compared with beta-lactam antibiotics because of slow killing, development of low-level resistance and poor tissue penetration. Though there have been documented instances of vancomycin-resistant staph and VISA, the low levels of resistance to teicoplanin documented in Jamaica and other studies conducted in South Africa indicate that vancomycin is still an effective treatment for staph infections, while judicious use is needed to ensure its effectiveness. There is accumulating evidence that the new oxazolidinone, linezolid, may have better clinical effectiveness against MRSA than the glycopeptides (Wilcox et al., 2004; Wunderink et al., 2003) despite being a bacteriostatic agent, perhaps because of its excellent tissue distribution. Consequently, MRSA infections are a very clear example of the adverse clinical effects of multiple drug resistance. Compared with MSSA infections, they have a significantly increased mortality when adjusted for other comorbidities and alternative therapies are less effective (glycopeptides), more toxic (vancomycin) or more expensive (linezolid).

Physicians' attitudes towards MRSA

In a cross-sectional survey of 174 physicians from several specialties at the UHWI conducted between September 2008 and April 2009, Tenant et al. (2010) noted that most physicians considered antibiotic resistance to be an extremely important global problem (55 per cent) but less significant nationally (35 per cent). The authors identified widespread use of antibiotics (91 per cent), inappropriate empiric choices (79 per cent) and use of broad-spectrum agents (70 per cent) as factors important in producing resistance. Of note, hand washing was not considered to be important in reducing resistance. Useful interventions included access to current information on local resistance patterns (90 per cent), institutional specific antibiotic guidelines (89 per cent) and educational programmes (89 per cent). Antibiotic cycling (40 per cent) and restriction (35 per cent) were regarded as less helpful. Knowledge of resistance-prone antibiotics and MRSA was high, but was poor for other specific resistant organisms, some of which were noted previously. Thankfully, empiric therapy for common infections was appropriate in most cases. However, only 45 per cent of physicians indicated that they would de-escalate to a narrow-spectrum antibiotic guided by a microbiology report and consultants were more likely to de-escalate therapy than junior staff.

Conclusion

Since antibiotic use became widespread about 60 years ago, bacteria have steadily and routinely developed resistance. Control of the emergence of resistance in Jamaica and elsewhere will depend on new approaches to prudent antibiotic use in hospitals and clinics, based in part on improved surveillance for MDR bacteria, de-escalation when appropriate and better systems to encourage staff adherence to contact isolation procedures. Equally important will be the development of new drugs with narrower

spectra of activity aimed at known and potentially new targets, and the evolution of market conditions that favour their use. Multidrug resistance among MRSA in Jamaica appears to be proportionately lower than in some developed countries; however, local research has shown an increasing trend and suggests it is time for concerted action. Much of the molecular assessment of multidrug resistance is still in its fledgling status, and work has started to demonstrate the significant role that mobile genetic elements and/or environmentally-disseminated genes play in the increasing trend observed in both hospital and community settings.

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