Methicillin-Resistant *Staphylococcus aureus*: Past, Present, and – Too Much of a – Future

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Staphylococcus aureus is one of the most virulent and versatile human pathogens. Only 3 years after the introduction of penicillin in 1941, strains of *S. aureus* emerged that produce beta-lactamase and consequently inactivate penicillin. The resistant strains disseminated from hospitals into the community and today less than 5% of isolates remain sensitive to penicillin. Strains of methicillin-resistant *S. aureus* were detected in 1961, shortly after methicillin came into clinical use. Resistance to methicillin requires the presence of the *mecA* gene that encodes penicillin-binding protein 2a and confers resistance to all penicillins and cephalosporins. Methicillin-resistant strains have also become resistant to other antimicrobial agents. A 10 year survey conducted by the Centers of Disease Control showed that the rate of methicillin-resistance of *S. aureus*, isolated from intensive care unit patients, increased from 22.8% in 1987 to 56.2% in 1997 [1].

As the prevalence of MRSA was increasing, so the emergence of vancomycin intermediately resistant and totally resistant strains of *S. aureus* was anticipated, and indeed the first strain of VISA was isolated in Japan in 1997 [2]. Five years later, in July 2002, the first clinical infection with VRSA was reported from Pennsylvania, USA [3]. The isolate contained the *mecA* and *vanA* genes mediating methicillin and vancomycin resistance, respectively. The evolving epidemiology of MRSA may turn out to resemble the described one for penicillin-resistant *S. aureus*. MRSA has become a major nosocomial pathogen, first in tertiary care hospitals and subsequently spreading to community hospitals and long-term care facilities. Recently, multiple studies have indicated that the frequency of MRSA acquired in the community is increasing. A meta-analysis of 18 studies found a pooled MRSA colonization rate of 1.3% among community members, but there was significant heterogeneity among study populations [4]. Several risk factors for MRSA colonization were identified, including previous hospital admission, residency at nursing homes, persons in contact with healthcare personnel, and age over 70 [5]. Among 831 otherwise healthy children examined in a pediatric emergency department in Israel, 5 (0.6%) were colonized with MRSA, compared with 9 of 118 (7.6%) chronically institutionalized children ($P < 0.001$) [6]. In this study, older age and a family member who is a healthcare worker were risk factors for MRSA colonization. In addition, there have recently been reports of serious infections involving soft tissue in children due to truly community-acquired methicillin-resistant *S. aureus*; these organisms were genetically different from the described hospital-acquired MRSA strains and were usually susceptible to multiple alternative drugs [7].

MRSA = methicillin-resistant *Staphylococcus aureus*
VISA = vancomycin intermediate *S. aureus*
VRSA = vancomycin-resistant *S. aureus*

MRSA prevalence rates vary widely by locale and by type and size of hospital. It remains unclear why in some geographic areas such as Scandinavian countries the prevalence remains low (less than 1%), whereas in other areas (southern Europe, USA, Australia and Israel, among others) MRSA is endemic [8]. Very active control measures and stringent antimicrobial use practiced in the low prevalence countries may have contributed to this success rate and serves an important lesson. In a previous study, Samra and Gadba [9] reported a methicillin resistance rate of 41.6% of 692 blood culture isolates of *S. aureus* from hospitalized patients in Israel. A more recent study showed that their MRSA rate now approaches 45% [10], similar to that reported from other hospitals in this country [11]. Patients who have been colonized with MRSA in hospitals may introduce the organisms into long-term care facilities and can become reservoirs for the pathogen. A survey in a large Israeli long-term care facility found that 6.2% of the patients were MRSA carriers, and these resided predominantly in the subacute departments [12].

The primary body site for colonization of *S. aureus* is the anterior nares, from which the organism may spread to other body sites. Persons colonized with *S. aureus* are at increased risk of developing infections due to these strains and most infections arise from endogenously carried strains. *S. aureus* is a major cause of serious infections involving skin, soft tissue, the respiratory tract, bone, joint, and endovascular tissue. Morbidity and mortality from staphylococcal bacteremia and endocarditis are substantial. There is controversy regarding the relative virulence of MRSA and MSSA strains, but cumulative data suggest that patients infected with MRSA have a higher mortality rate than patients infected with MSSA, in addition to higher hospital expenses associated with treatment of MRSA infections [13].

Unfortunately, therapeutic options for patients with MRSA infections are limited. Vancomycin is the drug of choice but this drug is inconvenient to administer as it requires intravenous infusions that take 1 hour, irritates the veins, has limited volume of distribution, slow bactericidal action, and is expensive. Alternative or adjunctive drugs can be divided into two groups: older familiar drugs and newer agents. Among the first group are the fluoroquinolones, trimethoprim-sulfamethoxazole, aminoglycosides, clindamycin, fusidic acid and rifampin. Most of these drugs are not as effective as vancomycin, either because they have less anti-staphylococcal activity or because resistance develops easily. The recent emergence of VISA and heterogeneous vancomycin-susceptible strains underscores the need for new antibiotics. A number of new anti-staphylococcal drugs are available, including teicoplanin, quinupristin-dalfopristin, oxazolidinones, and daptomycin; a new tetracycline derivative, tigacycline, is in advanced stages of development. Linezolid, the first oxazolidinone antibiotic in use, has broad *in vitro* activity against Gram-positive bacteria, including activity against MRSA and VISA. One of the advantages of this drug is its 100% bioavailability, allowing for oral treatment and shortening of hospital stay. Another advantage is the average concentration exceeding the minimal inhibitory concentrations for susceptible pathogens throughout the 12 hour dosing interval. In a randomized, open-label trial comparing the efficacy of linezolid to vancomycin in patients with MRSA infections, there was no difference between the two treatment groups with respect to clinical cure rates or microbiologic success rates [14].

A very relevant contribution to the study of this subject is the report in this issue of *IMAJ* by Samra and associates [15]. To the best of our knowledge, theirs are the first published linezolid susceptibility data of MRSA strains in Israel. One hundred and fifty MRSA isolates from clinical specimens of hospitalized patients were tested for susceptibility to vancomycin, teicoplanin, pristinamycin (quinupristin-dalfopristin), linezolid and classic agents such as TMP-SMX, fusidic acid and other agents. All isolates were susceptible to vancomycin, teicoplanin, pristinamycin and linezolid, but the MIC value of linezolid was the lowest. Among the classic antibiotics, fusidic acid had the best *in vitro* activity with 96.7% of the tested strains susceptible, followed by TMP-SMX and minocycline. An interesting finding is the increase in TMP-SMX susceptibility in MRSA isolates, compared to previous reports. Further investigation may shed light on whether this trend is due to reduced clinical use of TMP-SMX or to other causes. These data may be of assistance to clinicians treating MRSA infections, adding linezolid to the armamentarium against MRSA. Emergence of resistant strains during linezolid treatment has been reported and should encourage physicians to use this antimicrobial only sparingly [16].

Alongside the efforts to develop new drugs, careful attention should be paid to the reduction of nosocomial spread of staphylococcal infection. Adherence to standard precautions cannot be over-accentuated, including hand decontamination before and after every single patient contact, preferably with an alcohol-based hand rub, contact isolation and barrier nursing [17]. Isolation of patients with MRSA in single rooms or cohorting is more difficult to implement in facilities with a high MRSA prevalence rate. However, this should be attempted, especially in high risk areas (e.g., neonatology and surgical units), as well as in instances where MRSA infection involves the respiratory tract and open wounds. Complementary strategies used to prevent MRSA surgical site infection are preoperative screening and elimination of nasal colonization in patients and healthcare workers. Increased vigilance regarding implementation of infection control guidelines and improved use of antimicrobials are absolutely essential to curb the increasing prevalence of infections due to multidrug-resistant organisms.

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MSSA = methicillin-susceptible *S. aureus*

TMP-SMX = trimethoprim-sulfamethoxazole

MIC = minimal inhibitory concentration

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