Hospital-acquired methicillin-resistant *Staphylococcus aureus*: Epidemiology, treatment and control

Coleman Rotstein MD FRCPC

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Antimicrobial-resistant organisms are an expanding problem, resulting in increased morbidity and mortality, prolonged hospital stay, and heightened health care costs for care and antimicrobial management. Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a major hospital-acquired, antimicrobial-resistant pathogen. MRSA not only colonizes hospitalized patients but has a propensity to produce more serious, life- threatening infection than methicillin-susceptible strains. Numerous risk factors, including antimicrobial use and proximity to a patient harbouring MRSA, have been linked to the acquisition of MRSA. Although vancomycin has been the mainstay of therapy for MRSA, failures have been reported due to reduced susceptibility to this agent. Other available therapeutic agents for MRSA include trimethoprim-sulfamethoxazole, tetracycline, fusidic acid, rifampin (in combination with other effective agents) and linezolid. Potential therapeutic agents that are currently under investigation include daptomycin, dalbavancin, tigecycline, ceftobiprole and iclaprim. Only enhanced infection control practices can halt the progressive transmission of MRSA in the hospital environment. However, such measures have not quite fulfilled their promise in clinical studies. Moreover, eradication of MRSA colonization is controversial and may promote greater resistance. A multidisciplinary approach to the prevention, containment and treatment of MRSA is necessary.

Key Words: *Infection control; Methicillin-resistant* Staphylococcus aureus*; Treatment*

Le staphylocoque doré méthicillinorésistant contracté en milieu hospitalier : L'épidémiologie, le traitement et le contrôle

Les organismes résistants aux antimicrobiens représentent un problème croissant responsable de morbidité et de mortalité, d'hospitalisations prolongées, de frais de santé plus élevés en matière de soins et de prise en charge antimicrobienne. Le staphylocoque doré méthicillinorésistant (SDMR) est devenu un important pathogène résistant aux antimicrobiens en milieu hospitalier. Non seulement colonise-t-il les patients hospitalisés, mais il a la propension de produire une infection plus grave constituant un danger de mort que les souches méthicillinosusceptibles. De nombreux facteurs de risque, y compris l'usage d'antimicrobiens et la proximité d'un patient atteint du SDMR, sont reliés à l'acquisition de SDMR. Bien que la vancomycine représente le traitement principal du SDMR, des échecs ont été constatés en raison de la diminution de la susceptibilité à cet agent. Il existe d'autres agents thérapeutiques contre le SDMR, comme le triméthoprim-sulfaméthoxazole, la tétracycline, l'acide fusidique, la rifampine (associée à d'autres agents efficaces) et la linézolide. Des agents thérapeutiques potentiels sont en cours d'investigation, soit la daptomycine, la dalbavancine, la tigécycline, le ceftobiprole et l'iclaprim. Seules des pratiques accrues de contrôle des infections peuvent interrompre la transmission progressive du SDMR en milieu hospitalier. Cependant, dans le cadre d'études cliniques, ces mesures n'ont pas vraiment rempli leurs promesses. De plus, l'éradication de la colonisation par le SDMR est controversée et pourrait favoriser l'accroissement de la résistance. Une démarche multidisciplinaire visant la prévention, l'endiguement et le traitement du SDMR s'impose.

Antimicrobial resistance represents a rapidly growing and frequently challenging issue for clinicians. Not only can low-level antimicrobial resistance in microorganisms rapidly increase to high-level resistance, but microorganisms that are primarily resistant to one antimicrobial agent may rapidly become resistant to many others, affecting entire classes of compounds and creating cross-resistance between drug classes.

Antimicrobial resistance has major implications for the health care system. It is associated with increased morbidity, mortality, length of hospital stay and health care costs (1). The greatest risk factors for acquiring an antibiotic-resistant infection are intensive exposure to antibiotics and proximity to persons harbouring resistant bacteria (2). Antibiotic resistance has been precipitated by antibiotic overprescribing, inappropriate prescriptions of antibiotics for nonbacterial infections, and the use of antibiotics in farm and animal products. In the United States, more than 190 million courses of antibiotics are prescribed in hospitals annually and 145 million courses are prescribed in the community setting (3). Of the hospital prescriptions, 25% to 45% are believed to be inappropriate, while in a community setting, 20% to 50% have been deemed inappropriate.

Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a major hospital-acquired pathogen over the past two decades worldwide (4). MRSA is currently the most commonly identified antibiotic-resistant pathogen in the United States (5). Recently, infection due to community-acquired MRSA has also been reported (6). It is therefore not surprising that the incidence of MRSA has also increased in Canadian health care institutions in the past few years.

EPIDEMIOLOGY OF MRSA IN CANADA

Based on information from the Canadian Nosocomial Infection Surveillance Program (CNISP), 83% of all MRSA isolates can be directly attributed to a specific origin, while the other 17% are of unknown origin (7,8). MRSA colonization or infection in Canada increased significantly from 1995 to 1999, from 0.46 to 4.12 cases per 1000 admissions (P=0.002). There

Division of Infectious Diseases and Department of Medicine, McMaster University and Hamilton Health Sciences, Hamilton, Ontario
Correspondence and reprints: Dr Coleman Rotstein, Henderson Site, 711 Concession Street, Hamilton, Ontario L8V 1C3. Telephone 905-574-3301, fax 905-389-0108, e-mail crotstei@mcmaster.ca

TABLE 1
Antibiotic treatment of methicillin-resistant *Staphylococcus aureus*

Oral therapy
Trimethoprim-sulfamethoxazole (for susceptible strains)*
Doxycycline (for susceptible strains)*
Fluoroquinolones (for susceptible strains)*
Fusidic acid*
Linezolid
Intravenous therapy
Vancomycin (alone or in combination with rifampin)*
Trimethoprim-sulfamethoxazole (for susceptible strains)*
Quinupristin-dalfopristin
Linezolid
Tigecycline (investigational in Canada)
Ceftobiprole (investigational in Canada)
Daptomycin (investigational in Canada)
Dalbavancin (investigational in Canada)

**Rifampin may be added, but no data are available to support that the combination improves clinical efficacy*

was a further increase to 4.4 cases per 1000 admissions in 2001. Specifically, MRSA infections increased from 0.25 cases per 1000 admissions in 1995 to 1.2 cases per 1000 admissions in 2001. In addition, rates in the province of Ontario have exceeded those in other provinces. In 1995, there were 0.6 cases per 1000 admissions, while in 1999, there were 6.5 cases per 1000 admissions (P=0.003) (7). Nevertheless, the prevalence of MRSA in Canada dramatically trails the level seen in the United States (9).

MRSA poses considerable problems for health care facilities by prolonging the length of stay of patients, increasing the economic burden through additional hospital costs for barrier precautions and surveillance to identify patients colonized with the organism, and producing negative effects on patient care by using contact isolation precautions (10). Kim et al (11) delineated the economic significance of MRSA in Canada by determining that a mean number of 14 additional hospital days were attributable to MRSA infection, with costs of $14,360 per patient. Also, the cost of isolating a colonized patient was assessed to be $1,363 per admission.

Not only does MRSA add an economic burden — increasing length of stay, and costs related to infection control and patient contact isolation — it also produces nosocomial infection more frequently than methicillin-susceptible *S aureus* (MSSA) (12,13). If MRSA was only found in colonized patients, there would be little cause for concern. However, it appears that MRSA has a propensity to produce more serious infection (14). Moreover, higher mortality rates have been associated with MRSA bacteremia, ranging from 49% to 63.8%, than with MSSA (20% to 32%) (15,16). Multivariant logistic regression analysis demonstrated that MRSA infection was an independent risk factor for mortality (OR 3.0 to 4.2) (17). Melzer et al (18) corroborated the aforementioned finding and demonstrated that MRSA nosocomial bacteremia produced a higher attributable death rate (11.8%) than that of MSSA (5.1%; P<0.001).

It is also necessary to recognize the risk factors for the acquisition of MRSA. Recognized risk factors include previous hospitalization, admission to an intensive care unit, prolonged hospital stay, proximity to another patient with MRSA, older age, invasive procedures, presence of wounds or skin lesions, and prior antimicrobial therapy (19-23). In fact, the use of fluoroquinolones has been implicated, and is highly associated with the emergence of fluoroquinolone-resistant *S aureus* and, subsequently, MRSA (24-27). It appears that for fluoroquinolones, the main antimicrobial target in Gram-negative organisms is the DNA gyrase enzyme. Ciprofloxacin binds quite avidly to this target and, thus, is quite effective against these organisms. On the other hand, in Gram-positive organisms, the main target for fluoroquinolones is the enzyme topoisomerase IV, and ciprofloxacin does not bind very well to this target, therefore facilitating the development of resistance. Thus, fluoroquinolone-resistant *S aureus* may arise, and these organisms may quickly acquire other resistance genes. Therefore, the *mecA* gene may readily be acquired by *S aureus*, and this, in turn, produces an altered penicillin-binding protein (2a) that has a very low affinity to bind methicillin. This results in MRSA. It is this gene, as well as other genetic determinants for resistance to other classes of antibiotics that are easily acquired by *S aureus* isolates, that are also resistant to ciprofloxacin. Moreover, although the risk of fluoroquinolone resistance is greatest with ciprofloxacin, it also exists with levofloxacin, gatifloxacin and moxifloxacin, which have greater activity against *S aureus* because of their avidity for topoisomerase IV. It should also be noted that the recently described community-acquired MRSA strains have also proven to be problematic in the hospital setting. In these strains, the *mecA* gene is part of the smaller staphylococcal cassette chromosome *mec* type IV that enhances its efficiency of transfer from organism to organism and increases the potential of MSSA to metamorphasize to MRSA. Moreover, the staphylococcal cassette chromosome *mec* type IV only confers resistance to beta-lactam antibiotics but does not include genes coding for multidrug resistance as found in the hospital-acquired MRSA strains that possess types I and II (28).

TREATMENT OF MRSA

Various antimicrobial agents have been used anecdotally in the treatment of MRSA infections (Table 1). Few clinical trials have been designed to determine the optimal antimicrobial therapy for MRSA infections. In many of the studies, vancomycin was considered to be the 'gold standard' to which all other agents were compared. Moreover, in the past few years, several new agents with enhanced in vitro activity (compared with vancomycin) against MRSA organisms have become available, but clinical experience with these drugs against serious MRSA infections is lacking.

Vancomycin

Compared with beta-lactam therapy, vancomycin therapy has been associated with slower clinical response and more prolonged duration of MSSA bacteremia (29,30). Vancomycin has produced a less-than-optimal, slow response in MRSA endocarditis, as demonstrated by Levine et al (31). Failure of vancomycin therapy has also been documented in the treatment of patients with bacteremia, osteomyelitis and septic arthritis. Howden et al (32) found that MRSA isolates possessed reduced susceptibility to vancomycin, and as a result, therapy with vancomycin in the aforementioned infections failed. Fifteen of 25 patients in the study had minimal inhibitory concentrations (MICs) of 2 mg/L, whereas 10 of 25 had MICs

of 4 mg/L (32). Based on in vitro susceptibility guidelines, all of these isolates should have been susceptible to vancomycin. Overtly, vancomycin-intermediate *S aureus* (MIC of 8 mg/L to 16 mg/L) and vancomycin-resistant *S aureus* have appeared, and are of greater concern (33,34).

Trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole has been used to treat a small number of patients with MRSA bacteremia, endocarditis and meningitis (35). However, in a randomized clinical trial (36), trimethoprim-sulfamethoxazole proved to be as effective as vancomycin for serious infections, including bacteremias due to MRSA (success in 21 of 21 versus 26 of 26 infections), but was less effective for the treatment of infections due to MSSA. Unfortunately, increasing resistance, of the order of 40% to 50% of MRSA isolates, has been reported in Canadian hospitals (7).

Fluoroquinolones

The rapid emergence of ciprofloxacin resistance in staphylococci, especially MRSA, has occurred since its introduction (37). Furthermore, fluoroquinolones select for MRSA from among heterogeneously methicillin-resistant populations in vitro, and fluoroquinolone use is associated with an increased risk of acquisition of MRSA as noted above (24,38). Nevertheless, the newer generation fluoroquinolones gatifloxacin and moxifloxacin appear to be more potent against *S aureus*, but previous experience with fluoroquinolone resistance in MRSA has dampened clinicians' enthusiasm to use these antibiotics to treat MRSA infections (39).

Tetracyclines

Both doxycycline and minocycline have been used alone or in combination with rifampin for the treatment of MRSA infections with some success (40).

Fusidic acid

Fusidic acid has been used intravenously in combination with vancomycin, an aminoglycoside or a fluoroquinolone in a small series of patients with a variety of MRSA infections (41). However, resistance to fusidic acid often emerges rapidly when the drug is used alone.

Rifampin

Rifampin has in vitro bactericidal activity against MRSA, but emergence of resistance arises quickly when the drug is used alone. As a result, rifampin is often combined with doxycycline, fusidic acid and trimethoprim-sulfamethoxazole (42). Although the combination of rifampin and vancomycin has been used successfully in the treatment of infections when vancomycin alone was inadequate, the combination of these drugs may be antagonistic in vitro (43,44).

Linezolid

Linezolid may be administered either intravenously or orally. In an open-label trial for suspected or known MRSA infections (skin, pneumonia, urinary tract and bacteremia), linezolid was shown to be comparable with vancomycin (45). In addition, Wunderink et al (46) published a retrospective analysis of two double-blind, randomized clinical trials that demonstrated the superior clinical response and survival of linezolid compared with vancomycin for MRSA nosocomial pneumonia. Moreover, linezolid was found by Kollef et al (47) to have superior efficacy to vancomycin in ventilator-associated pneumonia caused by MRSA (62.2% versus 21.2%, P=0.001) (47). Linezolid was also recently shown to be superior to vancomycin in a randomized, open-label trial (48) for complicated skin and soft tissue infections. For MRSA infections in the modified intention to treat and microbiologically evaluable patient populations, linezolid achieved statistically superior cure rates compared with vancomycin (71% versus 55.1%, P=0.002, and 88.6% versus 66.9%, P=0.0001, respectively) (48). This may seem surprising given that linezolid is a bacteriostatic agent while vancomycin is bactericidal. Nevertheless, the results particularly related to hospital-acquired and ventilator-associated pneumonia are not unexpected because linezolid achieves excellent penetration into epithelial lining fluid, whereas vancomycin does not (47).

Quinupristin-dalfopristin

Quinupristin-dalfopristin, a streptogramin compound, was compared with vancomycin for the treatment of hospital-acquired pneumonia caused by *S aureus* (49). In patients with MRSA pneumonia, quinupristin-dalfopristin achieved a response rate of 31% (six of 20), equivalent to that achieved by vancomycin (44% [eight of 18]) (49).

Daptomycin

Daptomycin, a novel lipopeptide antibiotic with bactericidal activity against MRSA, remains investigational in Canada. However, it has been approved by the United States Food and Drug Administration for the treatment of complicated skin and skin structure infections due to susceptible Gram-positive pathogens (50). However, this compound has limited penetration into pulmonary epithelial lining fluid and is inactivated by surfactant. In addition, there was a recent report (51) of a daptomycin-resistant MRSA bacteremic isolate that developed while on therapy with daptomycin.

Dalbavancin

Dalbavancin is a novel lipoglycopeptide that inhibits cell wall synthesis. It has potent in vitro activity against MRSA. Its unique pharmacokinetics support once-weekly intravenous dosing. It also has been used effectively to treat catheter-related bloodstream infections due to *S aureus*, including MRSA (52).

Other investigational agents with activity against MRSA

The glycylcycline compound tigecycline is bacteriostatic but has enhanced in vitro activity against both MSSA and MRSA (53). In a randomized dose comparison study, clinical cures were achieved in 67% and 74% of patients with skin and skin structure infections who received 25 mg or 50 mg daily of tigecycline intravenously, respectively (54). This drug appears to be another potent agent against MRSA. In addition, it also possesses activity against vancomycin-resistant enterococci and penicillin-resistant *Streptococcus pneumoniae* (53,55).

Ceftobiprole (56) is a beta-lactamase-stable cephalosporin with high affinity for the modified penicillin-binding protein 2a produced by the *mecA* gene in MRSA (57). Similarly, a modified carbapenem with enhanced activity against MRSA (58); the fluoroquinolone DW286, which is a naphthyridone (59); iclaprim, a dihydrofolate reductase inhibitor (60); and rifalazil (61) all possess in vitro activity against MRSA.

INFECTION CONTROL

As mentioned previously, factors such as poor infection control and isolation practices, antimicrobial pressure, transmission through contact due to overcrowding in hospitals and prolonged hospitalization increase the risk for the development of resistance. It appears that antimicrobial stewardship is somewhat beneficial in preventing the emergence of resistant organisms. Yet, it is only infection control practices that can halt the spread of resistant organisms, such as MRSA, once they are established within the hospital environment.

A variety of infection control measures have been recommended for the management of hospitalized patients with MRSA infection to prevent transmission of the organism (62). Recommendations have included contact isolation for infected patients in private rooms, which includes wearing gloves when entering patients' rooms, wearing gowns when there is significant contact with patients and handwashing after leaving patients' rooms (63); cohort nursing; and screening or surveillance to identify asymptomatic MRSA carriers. However, the effectiveness of these measures must be questioned in light of the use of resources and increased expenditures. MRSA has not been eradicated by infection control measures that have included barrier precautions and handwashing (64). Moreover, the incidence of MRSA appeared to increase in intensive care units from 36% in 1996 to 57.1% in 2002, despite the adoption of barrier precautions (65). Also, problems have arisen in adherence to infection control practices by health care workers. Boyce et al (66) showed that the mean compliance by health care workers in adhering to contact isolation procedures was only 40%. Furthermore, compliance with gloves and gowns was 65%, respectively, for each modality, but compliance with gloves, gowns and handwashing was only 28% in another study (67). Finally, appropriate infection control measures have not been substantiated in randomized clinical trials. Although some reports have suggested a benefit from single-room isolation or cohort nursing, in a systematic review (68), no well-designed studies were noted that allowed the role of isolation measures alone to be assessed. It should also be emphasized that the reports claiming some benefit of isolation procedures have been predominately retrospective, lacking in proper statistical analysis and generally undertaken in response to outbreaks rather than within areas of the hospital with endemicity. Therefore, it is not surprising that a prospective study within two English teaching hospitals failed to demonstrate benefit of single-room isolation or cohorting of patients to reduce cross-infection with MRSA (69). It appears that although contact isolation procedures and/or cohorting of patients colonized with MRSA are advocated by authoritative bodies, such as the Society for Healthcare Epidemiology of America (70), they may not be as efficacious in preventing the longitudinal transmission of MRSA in specific patient care areas, such as intensive care units. Also, these measures have proven to be costly. Perhaps, as suggested by some investigators, more effective means of infection control to prevent the spread of MRSA are necessary (69).

Screening or surveillance of high-risk patients for colonization by MRSA, followed by implementation of isolation or barrier precautions for those found to be colonized, has nevertheless been demonstrated to be effective in controlling MRSA outbreaks in hospitals and reducing nosocomial transmission (71,72). It appears that screening patients admitted to high-risk inpatient units, such as an intensive care unit, may actually reduce MRSA acquisition rates and, subsequently, infection rates (73). Thus, screening programs have proved to be cost-effective in limiting nosocomial transmission of MRSA (74). Targeted surveillance may be augmented by using an automated alert system to identify carrier patients (75).

Even more controversial is the concept of eradication of MRSA carriage. The decolonization of MRSA may assist in preventing the development of subsequent infections in patients. However, an important parameter to consider in eradication therapy is certainly the extent of colonization (ie, the number of discrete body sites colonized). The extent of colonization may certainly dictate the mode of eradication used. Thus, it may be more difficult to eradicate MRSA from individuals with topical therapy if colonized within the gastrointestinal tract and deep wounds. Moreover, the ideal compound to effectively eradicate MRSA remains to be determined. Even more irksome is the development of resistance to the agent used in the decolonization process. A variety of drugs, including topical and oral agents, have been tried for MRSA decolonization in hospitalized patients. Mupirocin ointment has been used as a topical agent, while the oral agents used were ciprofloxacin, trimethoprim-sulfamethoxazole, rifampin, novobiacin, minocycline and fusidic acid (76-81). Cutaneous colonization in these studies varied, as did eradication measured on day 14 post-therapy. In addition, there was no statistically significant advantage for eradication in MRSA infection in the one study in which it was reported (76). Finally, the concept of the emergence of resistance secondary to eradication therapy is vexing (80,81). As a result, Simor and Loeb (4) recommended that there are insufficient data to support the use of topical or systemic antimicrobial therapy for eradicating nasal or extranasal colonization with MRSA. Because eradication could not be guaranteed and the development of resistance to the decolonization agents would definitely be a bane to clinicians, this procedure is not advisable.

MRSA presents an excellent example of how antimicrobial-resistant organisms develop and spread in the hospital setting. It also exemplifies the difficulties that arise in controlling the spread and treating the infectious complications of resistant organisms. The greatest risk factors for acquiring an antibiotic-resistant organism such as MRSA are the intensive exposure to antibiotics and the failure to adhere to appropriate infection control practices. The prevalence of MRSA is certainly growing in Canada. This organism is not confined to health care facilities but is now emerging as a key community-acquired pathogen associated with skin and soft tissue infections. The treatment of infections caused by MRSA is evolving. Both oral and parenteral alternatives are necessary. Due to the burden of illness associated with MRSA, clinicians must be cautious about the overuse of our mainstays of therapy, including vancomycin. Therefore, the development of new antimicrobial agents effective against MRSA and their appropriate use is crucial.

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