The management of infection and colonization due to methicillin-resistant Staphylococcus aureus: A CIDS/CAMM position paper

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Methicillin-resistant Staphylococcus aureus (MRSA) is being seen with greater frequency in most hospitals and other health care facilities across Canada. The organism may cause life-threatening infections and has been associated with institutional outbreaks. Several studies have confirmed that MRSA infection is associated with increased morbidity and mortality compared with infections caused by susceptible strains, even when the presence of comorbidities is accounted for. Treatment of MRSA infection is complicated by the fact that these organisms are resistant to multiple antimicrobial agents, so treatment options are limited. The effectiveness of decolonization therapy (attempting to eradicate MRSA carriage) is also uncertain. This paper reviews the medical management of MRSA infections, discusses the potential role of decolonization and provides an overview of evidence to support recommended infection control practices.

Key Words: Methicillin resistance; MRSA; Staphylococcus aureus

Although there have been recent reports describing community-onset MRSA in the United States, CNISP data would suggest that MRSA remains predominantly a hospital-acquired pathogen in Canada (6). Nevertheless, it would seem reasonable to expect that an increase in MRSA rates in hospitals will eventually lead to spread of the organism in long term care facilities and the community. In Canada, community-acquired MRSA has been reported most frequently in western Canada, especially among native Aboriginals and intravenous drug users (9,10). Recognized risk factors for MRSA acquisition have included 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 (11-15).
If MRSA only colonized patients, there would be little reason for concern. However, 20% to 60% of patients identified as being colonized with MRSA in hospital subsequently develop an MRSA infection (12). Using standard criteria for identification of infections, CNISP data indicated that approximately 31% of patients with MRSA in Canadian hospitals were infected (7). In certain high risk populations, staphylococcal infections including bacteremia occur more frequently following colonization with MRSA than after colonization with susceptible strains of \( \text{S} \) \( \text{aureus} \) (16). Moreover, MRSA does not merely replace susceptible strains of \( \text{S} \) \( \text{aureus} \) as a hospital-acquired pathogen, but rather, it appears to add substantially to the total burden of nosocomial infections (17,18). Although the results are somewhat controversial, several studies have also indicated increased mortality and prolonged hospitalization associated with MRSA infections (19-21). After adjustment for comorbidities, methicillin resistance has been found to be a significant independent risk factor for mortality in bacteremic patients (21-23).

Several studies have also documented the economic impact of MRSA in hospitalized patients, demonstrating increased costs associated with managing infections and with the implementation of control measures (19,24,25). The average attributable cost of managing an MRSA infection in a Canadian hospital was estimated to be approximately $14,360, whereas costs associated with managing a patient with MRSA colonization were approximately $1,363 per hospital admission (25).

The first strain of \( \text{S} \) \( \text{aureus} \), an MRSA, with reduced susceptibility to vancomycin was reported from Japan in 1996 (26,27). Since then, such strains with vancomycin minimum inhibitory concentrations (MIC) of 8 µg/mL to 16 µg/mL (vancomycin-intermediate \( \text{S} \) \( \text{aureus} \) [VISA]) have been reported from several countries in southeast Asia, South America, Europe and the United States (28-30). Of even greater concern has been the recent identification of two infections caused by MRSA with high level resistance to vancomycin (MIC greater than 128 µg/mL; vancomycin-resistant \( \text{S} \) \( \text{aureus} \) [VRS]) mediated by the vanA gene determinant found in vancomycin-resistant enterococci (31,32). These developments have emphasized the need for appropriate use of glycopeptides and other antimicrobial agents in the management of patients with MRSA. This paper reviews options for the treatment of patients with MRSA infection or colonization. The treatment options should be considered appropriate for hospitalized patients as well as for out-patients, and for those residing in long term care facilities.

### TREATMENT OF MRSA INFECTION

Few clinical trials designed to determine optimal antimicrobial therapy for MRSA infection have been published (Table 1). In all of these comparative studies, vancomycin was considered to be standard therapy. Inclusion criteria, sites and severity of infection, and outcome measures varied from study to study. Each of the studies included relatively small numbers of patients with documented infection due to MRSA and failed to show any statistically significant differences between the agents evaluated. In the past few years, several new agents with in vitro activity against resistant Gram-positive organisms have become available but clinical experience with these drugs against serious MRSA infections, including bacteremia, is still limited.

### Glycopeptides

Vancomycin is currently considered the treatment of choice for serious MRSA infections (33-36). Unfortunately, vancomycin is potentially more toxic and probably less effective than a beta-lactam antibiotic would be if the infection were caused by a susceptible strain of \( \text{S} \) \( \text{aureus} \) (35,37-39). Vancomycin has a relatively slow bactericidal effect against staphylococci, thereby possibly reducing its clinical effectiveness (40). The emergence of vancomycin resistance in MRSA and in enterococci is an additional reason for concern (27,31,32,35). Teicoplanin, a glycopeptide agent structurally related to vancomycin, is as active in vitro as vancomycin against MRSA but does not appear to offer any significant advantages for the treatment of MRSA infections (Table 1) (41,42).

### Clindamycin

Clindamycin has been used successfully in a small number of patients infected with susceptible strains of MRSA (43). However, most MRSA strains are resistant to clindamycin (6,44,45) and the drug should probably not be used in the treatment of systemic or bacteremic infections where MRSA is known or suspected to be a pathogen. In addition,
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staphylococci resistant to macrolides should also be considered resistant to clindamycin based on the presence of rRNA methylases specified by erm genetic determinants (46).

Minocycline
Minocycline is a semisynthetic derivative of tetracycline with in vitro activity against many strains of MRSA. Resistance to tetracycline in MRSA is common in many parts of the world and may be associated with cross-resistance to doxycycline and minocycline (44,47). Minocycline has been used in the management of both infected and colonized patients with MRSA, although clinical experience with the drug in these settings has been limited. There have been case reports describing the successful treatment of MRSA endocarditis with minocycline in patients who had failed to respond to other antimicrobial agents (48,49).

Trimethoprim-sulphamethoxazole
Trimethoprim-sulphamethoxazole (TMP-SMX) has been used to treat a small number of patients with MRSA bacteremia, endocarditis and meningitis (50). In a randomized, controlled trial, TMP-SMX (used in 21 patients) was found to be as effective as vancomycin (used in 26 patients) for those with MRSA infections including bacteremias, although TMP-SMX appeared to be less effective for the treatment of patients with infection due to susceptible strains of S. aureus (Table 1) (51). Increasing resistance to TMP-SMX in MRSA has been reported, limiting its use (44). Currently, approximately 40% to 50% of MRSA isolates in Canadian hospitals are resistant to this agent (6).

Fluoroquinolones
When fluoroquinolones such as ciprofloxacin were first introduced into clinical practice, staphylococci were uniformly susceptible to this class of drugs. There was optimism about the role fluoroquinolones might play in the treatment of MRSA infections and the eradication of MRSA colonization (52). However, rapid emergence of ciprofloxacin resistance in staphylococci, especially in MRSA, occurred (53,54). Currently, the vast majority of MRSA isolates in Canada are resistant to ciprofloxacin (6).

More recently, newer fluoroquinolones with enhanced in vitro activity against Gram-positive organisms have become available. Although drugs such as moxifloxacin, gatifloxacin and gemifloxacin have enhanced activity against staphylococci and MRSA (MIC$_{90}$ 0.5 to 8.0 µg/mL) (55-58), there have been no published reports describing the use of these agents for the treatment of MRSA infections. Currently available fluoroquinolones are not recommended for the treatment of MRSA infections.

Rifampin
Rifampin has bactericidal in vitro activity against staphylococci, including MRSA (59). However, there is rapid emergence of resistance if this drug is used alone (60). Therefore, it has been suggested that if rifampin is to be used, it should be used in combination with another active agent. Such drug combinations may result in synergistic activity against staphylococci (61,62). The combination of rifampin and vancomycin has been used successfully in the treatment of infections where vancomycin alone appeared to fail (63). However, the combination of these two drugs may be antagonistic in vitro (64). The clinical relevance of this observation is uncertain but it has been recommended that combination therapy with rifampin be reserved for patients not responding to vancomycin alone (34).

Fusidic acid
Fusidic acid interferes with protein synthesis and is bactericidal against staphylococci at high concentrations (65). The drug is available topically, orally and as an intravenous formulation. Administration of the drug intravenously has been associated with significant toxicity (granulocytopenia, hepatotoxicity, thrombophlebitis). As with rifampin, resistance to fusidic acid often emerges rapidly when the drug is used alone, particularly when used to treat chronic infections (65-67). In a rabbit model of endocarditis due to MRSA, fusidic acid alone was ineffective and was associated with the emergence of resistance to the drug; no resistance emerged if fusidic acid was used in combination with vancomycin, although the combination was no more effective than vancomycin alone (67). In a small series of patients with a variety of MRSA infections, 67% of the infections were cured when intravenous fusidic acid was used in combination with vancomycin, an aminoglycoside, or a fluoroquinolone (68). However, resistance to fusidic acid in association with treatment failure has also been reported to occur in a patient with MRSA infection treated with a combination of vancomycin and fusidic acid (69). Consequently, the role of fusidic acid in the management of MRSA infections remains uncertain.

Quinupristin-dalfopristin
Quinupristin-dalfopristin is the first of the streptogramin compounds to become available. The combination of quinupristin and dalfopristin is synergistic and bactericidal against most Gram-positive cocci, including MRSA (70). The drug also appears to be active against most strains of lincosamide- and erythromycin-resistant MRSA (71). Only a parenteral formulation of quinupristin-dalfopristin is available.

There has been a small number of case reports, open label studies and clinical trials that have demonstrated the efficacy of quinupristin-dalfopristin in treating a variety of MRSA infections. In many patients, quinupristin-dalfopristin was given in combination with other drugs (such as vancomycin or rifampin) (70,72-74) and in some cases, the drug was used in patients who had failed prior therapy (74,75). In one multicentre, randomized, controlled trial, quinupristin-dalfopristin was compared with vancomycin for the treatment of nosocomial pneumonia (Table 1) (76). In the 38 patients in whom MRSA infection was identified, there was no significant difference in outcome with either agent. Two multicentre trials of quinupristin-dalfopristin in hospitalized patients with complicated skin and soft tissue infections were reported by Nichols et al (Table 1) (73). Although a total of 562 patients were enrolled in these studies, only 15 with documented MRSA infection were evaluable. No difference in outcome was found in the quinupristin-dalfopristin-treated group compared with those treated with vancomycin.

In the relatively short time since the introduction of quinupristin-dalfopristin, the development of streptogramin resistance in MRSA has been reported (77,78). In at least one case, resistance to quinupristin-dalfopristin emerged in an MRSA isolate with reduced susceptibility to vancomycin (78).

Linezolid
Oxazolidinones are chemically distinct synthetic antibacterial agents that inhibit protein synthesis by binding to the 50S
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ribosomal subunit and thereby inhibit the binding of mRNA to the ribosome at the initiation of translation. Linezolid is the first of this class of compounds to become available but there are several other related agents under development. The drug may be administered intravenously or orally. Linezolid is active in vitro against Gram-positive cocci, including staphylococci and MRSA, with MIC\(_{90}\) generally reported to be approximately 2 μg/mL (79). However, it is important to note that linezolid has bacteriostatic activity against staphylococci and there is no synergy in vitro if linezolid is combined with vancomycin or rifampin (80). Prolonged treatment with linezolid has been associated with the development of reversible thrombocytopenia and myelosuppression (81). Linezolid has been used for the treatment of a variety of MRSA infections, although there is still little experience with the use of this drug in bacteremic infections (82). Two cases of MRSA endocarditis failed to respond to treatment with intravenous linezolid but were subsequently treated successfully with other agents (83). The first clinical MRSA isolate resistant to linezolid was recently reported (84).

There have been two published randomized, controlled trials with linezolid in patients with MRSA infections (Table 1). Stevens et al (85) randomized 460 patients with suspected MRSA infections to receive either linezolid (600 mg bid) or vancomycin (1 gm bid). MRSA infection was confirmed in 128 evaluable patients; none of these patients was bacteremic. The two drugs demonstrated equal efficacy. Rubinstein et al (86) conducted a multicentre, randomized, controlled trial comparing linezolid with vancomycin for the treatment of nosocomial pneumonia. MRSA was recovered from 31 of the 296 patients enrolled in the study. No significant difference in outcome was found in this subset of patients (nor was there a difference in outcome for the entire study population). Preliminary results of a study comparing linezolid with vancomycin for treatment of hospitalized patients with MRSA infection indicated that patients randomized to treatment with linezolid could be discharged home earlier because of the availability of an oral formulation of the drug (87).

Investigational compounds

The mechanism of beta-lactam resistance in MRSA involves the production of penicillin-binding protein (PBP) 2a with low affinity to beta-lactam compounds specified by the mecA gene. However, new beta-lactams have recently been developed that appear to bind to PBP 2a in staphylococci. RWJ-54428 is an investigational parenteral cephalosporin that is able to bind to PBP 2a and has been found to be active against MRSA, including strains with reduced susceptibility to vancomycin (MIC\(_{90}\) less than 1.0 μg/mL) (88). New carbapenems (eg, L-695,256 and SM-17466) able to bind to PBP 2a with a high degree of affinity have also been developed. These drugs appear to be active in vitro against MRSA strains (89,90) and L-695,256 appears to be as effective as vancomycin in an animal model of endocarditis (89).

New glycopeptides are being evaluated, including a compound designated oritavancin (LY333328) which appears to have in vitro activity against MRSA comparable to that of vancomycin, but is more rapidly bactericidal (91). New oxazolidinone agents (such as AZD2563) are also being evaluated (92).

Glycylcyclines are derivatives of tetracycline or minocycline, and have been found to have activity against many tetracycline-resistant organisms, including MRSA (93).

Newer fluoroquinolones and desfluoroquinolones (eg, garenoxacin, formerly BMS 284756) have been developed with enhanced activity against Gram-positive organisms (94). These agents appear to be more active in vitro against staphylococci, including MRSA, than ciprofloxacin, levofloxacin and gatifloxacin. Sitafloxacin is an investigational fluorquinolone that has been used to treat MRSA infections in a small number of patients. In an open label study involving 11 patients with MRSA infections who failed therapy with a glycopeptide, treatment with sitafloxacin resulted in a successful outcome in four patients, treatment failure in six and indeterminate outcome in one patient (95).

Daptomycin (LY146032) is an acidic lipopeptide that inhibits synthesis of lipoteichoic acid. It appears to be bactericidal against staphylococci with in vitro activity that is comparable to that of glycopeptides such as vancomycin and teicoplanin (96,97). It has also been found to have activity against strains of MRSA with reduced susceptibility to vancomycin (97). Daptomycin appears to be effective in treating MRSA infections in a number of animal models but there is limited clinical experience, and concerns about toxicity may limit its use in humans (98,99).

Evernimicins are oligosaccharide antimicrobials with broad-spectrum activity against Gram-positive organisms. Evernimicin (formerly SCH 27899) is the first of this class of drugs to be evaluated, has been found to be active against MRSA (MIC\(_{90}\) less than 1.0 μg/mL), and also appears to be more potent in vitro than vancomycin and quinupristin-dalfopristin (100).

The available data for all of these investigational compounds are limited, and many of these drugs are currently undergoing phase II and III studies. Although the preliminary results with these agents are promising, further clinical studies are required in order to determine their comparative efficacy and safety, and to determine their potential role in the management of MRSA infections.

VISA and VRSA strains

The clinical experience in treating infections caused by VISA and VRSA is limited. However, thus far these strains have generally been susceptible to TMP-SMX, tetracycline and linezolid; one clinical isolate was reported to be resistant to quinupristin-dalfopristin (100).

There are clinical trials of eradication therapy in colonized patients or as part of infection control strategies to limit transmission of the organism in health care settings. There are clinical trials of eradication therapy in hospitalized patients. An important consideration in evaluating the efficacy of treatment to eradicate MRSA is the extent of colonization. It may be more difficult to eradicate MRSA from individuals with extranasal sites of colonization such as the perineum, wounds or catheter exit sites (105). Other relevant factors include the susceptibility of the MRSA strain to the antimicrobial agent being used for

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decolonization. Moreover, persistence of MRSA colonization may actually be due to the acquisition of a new strain of MRSA rather than failure of eradication therapy. These factors need to be considered when evaluating the efficacy of antimicrobial agents for eradicating MRSA colonization.

Six randomized, controlled trials of topical or systemic agents used for MRSA decolonization in hospitalized or long term care facility patients have been reported (53,105-109) and are summarized in Table 2. A variety of drugs was used, including topical and oral agents. Three of the trials included a placebo or no treatment group. The percentage of patients with nasal MRSA colonization alone was reported in five studies and ranged from 26% to 100% (105-109). Percentages of cutaneous site (including ischemic or decubitus ulcers) colonization were reported in four studies and ranged from 7% to 46% (105,106,108,109). Eradication of MRSA on day 14 post-treatment was the most frequently reported outcome. Only one study reported the occurrence of MRSA infection (105). Five of the studies were conducted in acute care hospitals (53,105,106,108,109) and one in long term care facilities (107). No statistically significant difference in overall MRSA eradication was identified in any of the studies, although most were small and not adequately powered. The confidence intervals were generally wide and do not exclude clinically important effects. In one study, mupirocin was found to be less effective in eradicating extranasal MRSA than was topical fusidic acid and oral TMP-SMX (108).

Only one study reported data regarding MRSA infection as an outcome: Harbarth et al (105) randomized 102 patients in a Swiss university hospital to five days of treatment with mupirocin ointment or to placebo. Ten MRSA infections occurred (five skin or wound infections, four urinary infections and one osteomyelitis). Three (7%) infections were in the mupirocin group and seven (14%) in the placebo group (RR 0.47; 95% CI 0.13 to 1.70).

These clinical trials also examined the emergence of antimicrobial resistance to the agents used. In one study, strains with low level resistance to mupirocin (MIC 8 to 64 µg/mL) were documented in 23 participants (11 in the mupirocin group and 12 in the placebo group) but no isolates demonstrated higher levels of resistance (110). In the study by Chang et al (109), all pretreatment isolates were susceptible to fusidic acid but, following treatment with this agent, resistance developed in two strains. Similarly, Muder et al (107) found increased rifampin MICs in four patients receiving rifampin, and an increase in minocycline MICs was noted in post-therapy isolates from three patients. Resistance to ciprofloxacin and rifampin developed in MRSA isolates from patients treated with these drugs (53). In contrast, none of the strains from 12 patients treated with either mupirocin or fusidic acid and

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>n</th>
<th>Interventions</th>
<th>Length of follow-up (days)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>53 (1990)</td>
<td>21</td>
<td>Ciprofloxacin + rifampin &gt;14 days vs TMP-SMX</td>
<td>180</td>
<td>30% eradication with ciprofloxacin vs 40% with TMP-SMX (RR 0.6; 95% CI 0.2 to 1.9)</td>
</tr>
<tr>
<td>106 (1993)</td>
<td>80</td>
<td>Novobiocin + rifampin &gt;7 days vs TMP-SMX</td>
<td>14</td>
<td>67% eradication with novobiocin vs 53% with TMP-SMX (RR 1.3; 95% CI 0.9 to 1.6)</td>
</tr>
<tr>
<td>107 (1994)</td>
<td>35</td>
<td>Rifampin &lt;5 days vs minocycline × 5 days vs rifampin + minocycline × 5 days vs no treatment</td>
<td>90</td>
<td>70% eradication with rifampin vs 14% with no treatment (RR 4.9; 95% CI 0.8 to 31.5); 38% eradication with minocycline vs 14% with no treatment (RR 2.6; 95% CI 0.35 to 19.9); 50% eradication with rifampin + minocycline vs 14% with no treatment (RR 3.5; 95% CI 0.5 to 23.8)</td>
</tr>
<tr>
<td>108 (1995)</td>
<td>72</td>
<td>Mupirocin ointment ×5 days vs fusidic acid ointment + TMP-SMX ×5 days</td>
<td>90</td>
<td>74% eradication with mupirocin vs 71% fusidic acid + TMP-SMX (RR 1.1; 95% CI 0.6 to 1.9)</td>
</tr>
<tr>
<td>105 (1999)</td>
<td>102</td>
<td>Mupirocin ointment vs placebo ×5 days</td>
<td>26</td>
<td>25% eradication with mupirocin vs 18% with placebo (RR 1.4; 95% CI 0.6 to 3.0)</td>
</tr>
<tr>
<td>109 (2000)</td>
<td>16</td>
<td>Fusidic acid orally ×7 days vs no treatment</td>
<td>14 to 77</td>
<td>33% eradication with fusidic acid vs 50% with no treatment (RR 0.7; 95% CI 0.2 to 2.4)</td>
</tr>
</tbody>
</table>

**TABLE 2**

Summary of characteristics and results of clinical trials of antimicrobial agents used for eradication of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization

*TMP/SMX* Trimethoprim-sulphamethoxazole; *Vs Versus*
patients with MRSA are cost effective in limiting nosocomial outbreaks in hospitals and long term care facilities (115-119), and in reducing nosocomial transmission and overall prevalence in facilities where MRSA is endemic (11,110,120-125). Jernigan et al (118) reported that contact isolation (private room; use of gloves for manual contact with the patient or potentially contaminated surfaces; gown use for direct patient contact; mask worn when within 1.5 m of the patient) interrupted nosocomial transmission of MRSA. MRSA transmission was 16 times more frequent from nonisolated patients compared with those in isolation.

Screening and surveillance
Studies have demonstrated that isolation of patients identified as having MRSA from clinical specimens only was unsuccessful in controlling MRSA transmission or reducing nosocomial MRSA rates (11,114). In contrast, screening high risk patients for the presence of MRSA followed by implementation of isolation or barrier precautions for those found to be infected or colonized has been shown to be effective in controlling MRSA outbreaks in hospitals and long term care facilities (115-119), and in reducing nosocomial transmission and overall prevalence in facilities where MRSA is endemic (11,110,120-125). Jernigan et al (118,121) reported a 15-fold decrease in transmission of MRSA in a hospital when colonized patients were recognized by a screening program and then cared for with isolation precautions, compared with when isolation precautions were used only in patients recognized to have MRSA from clinical specimens. Screening patients admitted to a high risk in-patient unit, such as an intensive care unit, was found to be successful in reducing MRSA acquisition rates from 5.8% to 2.6% (P<0.002) and this was associated with a significant decrease in MRSA infection rates (123). Several studies have also documented that screening programs to identify colonized patients with MRSA are cost effective in limiting nosocomial transmission of MRSA (121,124,126).

Although extremely variable, MRSA carriage tends to be prolonged, for months or even years. The half-life of MRSA colonization in patients previously known to have been MRSA carriers and then subsequently readmitted to hospital has been estimated to be approximately 40 months (127). Therefore, it has been recommended that an ‘alert’ system be implemented to identify patients previously known to have had MRSA on readmission to hospital so that they can be screened and placed into isolation if appropriate. Outcomes associated with this recommendation have not been evaluated.

Isolation and barrier precautions
Contamination of the inanimate hospital environment of patients with MRSA occurs frequently. In one study, 69% to 73% of the rooms with MRSA patients were contaminated (128). Moreover, the gloved hands of personnel entering the rooms of MRSA patients frequently became contaminated by touching contaminated environmental surfaces even without direct contact with patients (128). Gowns worn by health care providers also often became contaminated. These findings support recommendations for use of a private room, gloves and gowns when caring for patients with MRSA infection or colonization. Jernigan et al (118) reported that MRSA transmission occurred both from nonisolated patients and from healthcare providers who had contact with MRSA patients. Therefore, it has been recommended that an ‘alert’ system be implemented to identify patients previously known to have had MRSA on readmission to hospital so that they can be screened and placed into isolation if appropriate. Outcomes associated with this recommendation have not been evaluated.

Decolonization of colonized patients or staff
Decolonization therapy of colonized hospital in-patients has been used to reduce the reservoir of MRSA during outbreaks (129-131). This strategy has been effective when combined with other interventions including MRSA screening and implementation of barrier precautions. Similarly, decolonization therapy of hospital health care providers with nasal MRSA colonization has also been used as part of outbreak management (129,130,132). However, because decolonization therapy has invariably been implemented concurrently with other interventions, it is difficult to determine the attributable effect of this strategy.

RECOMMENDATIONS
Specific recommendations for the management of patients infected or colonized with MRSA are listed below. The recommendations have been classified into five levels based on the quality of evidence (Table 3) and have been used previously in Position Papers of the Canadian Infectious Disease Society
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**Table 3**

**Classification of level of evidence for recommendations**

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Level I</td>
<td>Based on randomized, controlled trials (or meta-analysis of such trials) of adequate size to ensure a low risk of incorporating false-positive or false-negative results</td>
</tr>
<tr>
<td>Level II</td>
<td>Based on randomized, controlled trials that are too small to provide Level I evidence. These may show either positive trends that are not statistically significant or no trends, and are associated with a high risk of false-negative results</td>
</tr>
<tr>
<td>Level III</td>
<td>Based on nonrandomized, controlled or cohort studies, case series, case controlled studies or cross-sectional studies</td>
</tr>
<tr>
<td>Level IV</td>
<td>Based on the opinion of respected authorities or that of expert committees as indicated in published consensus conferences or guidelines</td>
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</tbody>
</table>

This classification scheme has been previously used in Canadian Infectious Disease Society Position Papers (133)

**REFERENCES**


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