Community-associated methicillin-resistant Staphylococcus aureus infection

Literature review and clinical update

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Abstract

Objective To provide information on the prevalence and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections and the distinction between community-associated MRSA and health care–associated MRSA.

Quality of evidence The MEDLINE and EMBASE databases were searched from 2005 to 2016. Epidemiologic studies were summarized and the relevant treatment literature was based on level I evidence.

Main message The incidence of community-associated MRSA infection is rising. Certain populations, including indigenous Canadians and homeless populations, are particularly affected. Community-associated MRSA can be distinguished from health care–associated MRSA based on genetic, epidemiologic, or microbiological profiles. It retains susceptibility to some oral agents including trimethoprim-sulfamethoxazole, clindamycin, and tetracyclines. Community-associated MRSA typically presents as purulent skin and soft tissue infection, but invasive infection occurs and can lead to severe, complicated disease. Treatment choices and the need for empiric MRSA coverage are influenced by the type and severity of infection.

Conclusion Community-associated MRSA is a common cause of skin and soft tissue infections and might be common in populations where overcrowding and limited access to clean water exist.

Infection à Staphylococcus aureus résistants à la méticilline d’origine communautaire

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Résumé

Objectif  Fournir des renseignements sur la prévalence et le traitement des infections aux Staphylococcus aureus résistants à la méticilline (SARM), de même que sur la distinction entre les SARM d’origine communautaire et les SARM associés aux soins de santé.

Editor’s Key Points

• Isolates of methicillin-resistant Staphylococcus aureus (MRSA) that were first identified as hospital acquired are called health care–associated MRSA and are highly antibiotic resistant. Isolates of MRSA that appear in young and otherwise healthy patients are identified as community–associated (previously community-acquired) MRSA (CA-MRSA). Neither of these bacteria exist solely in the community or in hospitals.

• Empiric treatment is the norm for these typically purulent skin and soft tissue infections and includes consideration of severity of illness, access to follow-up, and patient adherence. Clinical practice guidelines for CA-MRSA treatment recommend increasingly aggressive treatment with increased severity of infection.

• Predisposing factors for CA-MRSA infection are varied and include living in a group setting, participation in sports teams, and social determinants of health. Crowded living environments and lack of access to clean water are also associated with increased risk of CA-MRSA infection.

Points de repère du rédacteur

• Les isolats des Staphylococcus aureus résistants à la méticilline (SARM), initialement identifiés comme étant d’origine nosocomiale, sont appelés les SARM associés aux soins de santé et ont une forte résistance aux antibiotiques. Les isolats des SARM détectés chez des patients jeunes et autrement en santé sont connus sous le nom de SARM d’origine communautaire (auparavant acquis dans la communauté – SARM-AC). Ni l’une ni l’autre de ces bactéries n’existe que dans la communauté ou dans les hôpitaux.

• Un traitement empirique est la norme pour ces infections de la peau et des tissus mous, typiquement purulentes; il comporte la prise en compte de la gravité de la maladie, l’accès à un suivi et l’observance du traitement par le patient. Les guides de pratique clinique concernant le traitement des SARM d’origine communautaire recommandent une thérapie proportionnelle à la sévérité de l’infection.

• Parmi les divers facteurs qui prédisposent à une infection aux SARM d’origine communautaire figurent la vie en groupe, la participation à des sports d’équipe et les déterminants de santé. La vie dans un environnement surpeuplé et le manque d’accès à de l’eau potable sont aussi associés à un risque accru d’infection aux SARM d’origine communautaire.

This article has been peer reviewed.

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**Quality of evidence**

In MEDLINE and EMBASE (2005 to 2016), the term *methicillin-resistant Staphylococcus aureus* was combined with the MeSH terms *abscess* or *synovial fluid* or *cerebrospinal fluid* or *shock* or *septic or bacteremia or skin diseases, bacterial or soft tissue infections or skin and soft tissue infections, and incidence.*

The abstracts or titles of generated papers were read for relevance to the review topic. Additional papers were extracted from reference lists. A total of 85 relevant articles were chosen for this review. Most of the recommendations of the Infectious Diseases Society of America were based on level II or level III evidence. We have identified any level I evidence support for treatment-related findings.

**Main message**

*Staphylococcus aureus* is a common component of skin flora, and 30% to 50% of healthy adults are colonized with it at any given time. Preferred colonization sites include the axillae, anterior nares, pharynx, vagina, rectum, and perineum, and damaged skin. Colonization with *S aureus* is a commensal, asymptomatic relationship. Symptomatic *S aureus* infection is less common and might occur following breaks in skin or mucosal barriers. Its severity is influenced by isolate virulence and host factors. Diseases caused by *S aureus* range from superficial skin and soft tissue infections (SSTIs) to life-threatening invasive disease, including bacteraemia, endocarditis, and toxic shock syndrome. Most *S aureus* infections are caused by methicillin-sensitive *S aureus* (MSSA), which responds to penicillin. Methicillin-resistant *S aureus* infections predominate (75%) in tertiary care centre staphylococcal infections, while some rural hospitals report MRSA accounts for slightly more than half (56%) of staphylococcal infections. This review will concentrate on strains that are resistant to penicillin (MRSA), for which *methicillin* (or *oxacillin*) is the term used by laboratories to identify penicillin resistance.

**Methicillin-resistant *S aureus*: 2 distinct origins.**

Methicillin-resistant *S aureus* was first identified at a hospital in the United Kingdom in 1961, shortly after the introduction of methicillin. In Canada, MRSA was first documented in 1964 and the first outbreak occurred in 1978 at the Royal Victoria Hospital in Montreal, Que. From the time of its emergence until the 1980s, MRSA was essentially a hospital-acquired pathogen. Today, these isolates of MRSA are called *health care-associated MRSA* (HA-MRSA) and are highly resistant to most oral antibiotics.

In the late 1980s and early 1990s cases of MRSA in young and otherwise healthy patients without any health care–related risk factors were reported. Some of the earliest reports of such infections in Canada and Australia came from isolated indigenous communities. Today, these isolates of MRSA have been identified as *community-associated* (previously *community-acquired*) MRSA (CA-MRSA).

Community-associated MRSA and HA-MRSA can be differentiated in several ways. These include presumed location of acquisition (ie, community or hospital), antibiotic susceptibility pattern, and genotyping, the latter being the most definitive. Our review included many articles with genotyped definitions, but some smaller studies use antibiotic susceptibility patterns.

Some newer, highly resistant strains have arisen, but they are rare in Canada and are currently limited to tertiary care centres. They include vancomycin-intermediate *S aureus* (VISA), heterogeneous VISA, and vancomycin-resistant *S aureus*. 

**Conclusion**

Les SARM d’origine communautaire sont une cause fréquente d’infection de la peau et des tissus mous et peuvent être courants dans les populations surpeuplées et où l’accès à l’eau potable est limité.

**Methicillin-resistant** *Staphylococcus aureus* is recognized in the popular press as a “superbug.” Medically, it is a common bacterium that can affect clinical care in important ways. Much of what we know about MRSA has been discovered in the past 30 years. The purpose of this literature review is to describe the evolving knowledge about MRSA and its associated risk factors and epidemiology, and to provide an update on best practices for family physicians.
Comparing CA-MRSA and HA-MRSA. Community-associated MRSA and HA-MRSA are genetically, epidemiologically, and phenotypically distinct (Table 1).2,4,6-8,10-15,19,22-34

Contemporary advances in laboratory technology have demonstrated that methicillin resistance was acquired through different genes in CA-MRSA and HA-MRSA isolates. Specifically, staphylococcal chromosomal cassette mec (SCCmec) types I, II, and III confer methicillin resistance in HA-MRSA whereas SCCmec types IV and V confer methicillin resistance in CA-MRSA.2,23-27

The SCCmec types carried by CA-MRSA are larger than those carried by CA-MRSA and confer resistance to additional non–β-lactam antibiotics. Community-associated MRSA is therefore susceptible to a broader range of antibiotics than HA-MRSA is.2,4,6-8,10-15,19,22-34 A study of pathogens isolated at Canadian hospitals between 2007 and 2009 found the susceptibility of CA-MRSA to trimethoprim-sulfamethoxazole (100.0%), gentamicin (98.7%), and clindamycin (86.1%) to be greater than that of HA-MRSA (86.5%, 85.5%, and 27.8%, respectively).4 Antibiotic sensitivity profiles can consequently be used as an inexpensive means of classifying MRSA as health care associated or community associated.16,35 For example, clindamycin susceptibility is predictive of CA-MRSA with 95% sensitivity, 80% specificity, and a likelihood ratio of 4.86.36 Methicillin-resistant S. aureus isolates that are resistant to 3 or more non–β-lactam antibiotics can safely be categorized as HA-MRSA.16

Before advances were made in laboratory genetic technologies, epidemiologic risk factors were used to differentiate cases of HA-MRSA and CA-MRSA infection: the location of acquisition (ie, community or hospital) provided its designation.26,27 In the contemporary context, this method of differentiating HA-MRSA and CA-MRSA no longer aligns with clinical reality, as CA-MRSA has found its way into hospitals and is becoming an increasingly prevalent hospital pathogen.2,32 An American study found that community-associated strains of MRSA are increasing both in communities and in hospitals.15 In Canada, more than 20% of nosocomial MRSA infections are caused by CA-MRSA.17,30 A recent study from Alberta found 27.6% of such hospital-onset MRSA infections were caused by CA-MRSA and 27.5% of community-associated infections were caused by HA-MRSA.36 Both communities and hospitals have become antibiotic-rich environments and are apparently exchanging bacterial isolates.

**Table 1. Comparison of CA-MRSA and HA-MRSA**

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time and location of emergence</td>
<td>1980s-1990s, in the community</td>
<td>1960s, in hospitals</td>
</tr>
<tr>
<td>Genotype</td>
<td>SCCmec types IV and V</td>
<td>SCCmec types I, II, and III</td>
</tr>
<tr>
<td>Virulence factors</td>
<td>Panton-Valentine leukocidin often present; other virulence factors believed to exist</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Common subtypes</td>
<td>CMRSA-10 (USA300), CMRSA-7 (USA400)</td>
<td>CMRSA-2 (USA100)</td>
</tr>
<tr>
<td>Predominant type of infection</td>
<td>Skin and soft tissue infections</td>
<td>Respiratory tract, urinary tract, bloodstream, and postsurgical infections</td>
</tr>
<tr>
<td>Infection onset</td>
<td>Typically in the community in young, healthy individuals</td>
<td>Typically in hospital, often associated with older age, intensive care unit stay, and central lines</td>
</tr>
<tr>
<td>Antibiotic susceptibility</td>
<td>Susceptible to a range of antibiotics</td>
<td>Limited range of antibiotic susceptibility</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Community risk factors(^{25,34})</td>
<td>Health care risk factors(^{26,27})</td>
</tr>
<tr>
<td></td>
<td>• Living or working in a group setting (such as military barracks, subsidized housing, or a shelter)</td>
<td>• Surgery, hospitalization, residence in a long-term care facility, or dialysis within the past 12 months</td>
</tr>
<tr>
<td></td>
<td>• Use of illegal drugs within the past year</td>
<td>• The presence of an indwelling percutaneous catheter</td>
</tr>
<tr>
<td></td>
<td>• History of CA-MRSA infection or colonization</td>
<td>• Being hospitalized for more than 48 hours at time of first positive culture</td>
</tr>
<tr>
<td></td>
<td>• Regular contact with somebody who lives or works in a group setting, has used drugs in the past year, or has a history of CA-MRSA</td>
<td>• Being HIV positive</td>
</tr>
<tr>
<td></td>
<td>• Absence of in-home water service</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Recent antibiotic use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Being HIV positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Playing contact sports</td>
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</table>

There is consistent evidence that CA-MRSA is more likely than HA-MRSA to be associated with SSTIs. Community-associated MRSA is more likely than HA-MRSA to carry Panton-Valentine leukocidin, a known virulence factor often associated with tissue necrosis SSTIs.

Methicillin-resistant *S. aureus* SSTIs are associated with higher mortality rates, longer hospital admissions, and greater hospital costs than SSTIs caused by MSSA strains are. The reason for this is unclear, but might involve greater virulence of MRSA relative to MSSA or increased effectiveness of β-lactam antibiotics against MSSA.

In 2012, Golding reported a high rate of CA-MRSA infection in northern Saskatchewan (168.1 cases per 10,000 population in 2006). A compilation of 8 years of data from this region, including 2731 cases, shows that most cases (78.2%) are SSTIs, followed distantly by ear infections (6.7%), urogenital infections (2.4%), respiratory infections (1.1%), and joint or blood infections (0.4%) (Figure 1).

A community and hospital study done in northern Ontario documented that 56% of the burden of staphylococcal illness was caused by CA-MRSA.

The predominant strains of CA-MRSA identified are Canadian epidemic strain (CMRSA)-10 (also known as USA300) and CMRSA-7 (also known as USA400). The predominant strain of HA-MRSA is CMRSA-2 (also known as USA100). Health care-associated MRSA is more likely to be associated with respiratory tract, urinary tract, bloodstream, and postsurgical infections.

**Risk factors.** The original epidemiologic definition of HA-MRSA infection captures its principal risk factors: hospitalization, other prolonged exposure to a health care environment, or the presence of a percutaneous device such as a central line.

Predisposing factors for CA-MRSA infection are more varied and are intimately associated with social determinants of health. Frequent skin-to-skin contact, wound contact, and poor sanitation facilitate the transmission of CA-MRSA. Crowded living environments, including military barracks, homeless shelters, subsidized housing, and prisons, are associated with increased risk of CA-MRSA infection. A study of the relationship between in-home pressurized water service and infectious diseases among Alaska Natives found that regions with limited access to clean water had significantly higher rates of MRSA infections (rate ratio = 7.1; 95% CI 3.6 to 14.0) and hospitalization for skin infections (rate ratio = 2.7; 95% CI 1.8 to 4.1). Socially disadvantaged minority populations are consistently associated with higher rates of CA-MRSA infection, including African Americans, Canadian First Nations communities, and the indigenous populations of Australia and New Zealand. Homelessness is another recognized risk factor for CA-MRSA infection, as is intravenous drug use.

**Epidemiology.** During the 2000s, increasing incidence rates of CA-MRSA infections were widely reported by researchers in the United States and Canada, along with a corresponding increase in SSTIs caused by *S. aureus*. Rates of

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**Figure 1. Rates of community-associated methicillin-resistant *Staphylococcus aureus* infections in northern Saskatchewan: N = 2731.**

- Skin and soft tissue infections
- Ear infections
- Urogenital infections
- Respiratory infections
- Joint or blood infections
- Not specified
CA-MRSA infection are increasing, while HA-MRSA infection rates are generally reported to be in decline.\textsuperscript{19,53,57}

Several studies documenting the epidemiology of MRSA in indigenous populations have been published. Studies from communities in the United States,\textsuperscript{5,34} Canada,\textsuperscript{6,19,39,41,50,51} Australia,\textsuperscript{11,16} and New Zealand\textsuperscript{52} demonstrate high and increasing rates of CA-MRSA infection in the indigenous populations, where HA-MRSA is rare.

In Canada, Muileboom et al found the proportion of \textit{S aureus} isolates demonstrating methicillin resistance isolated from cultures obtained in one northern Ontario laboratory increased from 31\% in 2008 to 56\% in 2012.\textsuperscript{5} Kirlew et al reported an incidence rate of MRSA bacteremia of 41.1 cases per 100000 person-years in northwestern Ontario.\textsuperscript{51} In northern Saskatchewan, Golding et al found that the rate of CA-MRSA infection increased from 8.2 cases per 10000 person-years in 2001 to 168.1 cases per 10000 person-years in 2006.\textsuperscript{41} A previous study found that 99.5\% of MRSA isolates from these remote communities were CA-MRSA.\textsuperscript{60} A 1-year study at the Children’s Hospital of Winnipeg in Manitoba found that 79\% of patients from outside of Winnipeg who presented with community-onset \textit{S aureus} infection lived in rural communities in northern Manitoba, southern Nunavut, or northwestern Ontario.\textsuperscript{39} Among these patients, the rate of MRSA infection was relatively high (61\%).\textsuperscript{39} A large study assessing MRSA infection rates among children across Canada between 1995 and 2007 found that 25\% of all cases occurred in First Nations children.\textsuperscript{19}

Like their counterparts in Canada, indigenous populations in the United States, Australia, and New Zealand face disproportionately high rates of MRSA-associated infection and hospitalization.\textsuperscript{6,11,16,52}

The confluence of environmental and host factors might explain the disproportionate MRSA burden in indigenous communities. Environmental conditions associated with social and material deprivation, such as overcrowding and inadequate access to in-home pressurized water service, are associated with the transmission of MRSA and the development of MRSA-associated SSTIs.\textsuperscript{34} These same environmental conditions are pressing concerns in indigenous communities around the world.\textsuperscript{11,16,34,51} Additionally, the prevalence of host factors increasing vulnerability to infection by modulating the immune response (such as diabetes mellitus) or providing a portal of entry (skin disease, injection drug use) might be elevated in some indigenous communities.\textsuperscript{59,63}

\textbf{Treatment.} Empiric treatment is the norm for infections and must take into consideration information about likely infecting agents, severity of illness, access to follow-up, patient adherence, and other factors. Published guidelines, original research, and knowledge of local epidemiology might assist clinicians in making clinical judgments that adhere to principles of antimicrobial stewardship.\textsuperscript{32,62-65} The current clinical practice guidelines for CA-MRSA and HA-MRSA treatment from the Infectious Diseases Society of America recommend increasingly aggressive treatment with increased severity of infection.\textsuperscript{66}

A distinction is made between purulent and nonpurulent SSTIs. Uncomplicated abscesses without evidence of systemic toxicity might be treated by incision and drainage without antibiotics (level I evidence).\textsuperscript{22,28,65} Evidence from 3 randomized controlled trials and a systematic review indicates not providing antibiotics to patients who undergo incision and drainage for uncomplicated abscesses is associated with lower reinfection rates and comparable wound healing (level I evidence).\textsuperscript{22,66-69} Empiric treatment of purulent cellulitis, when needed, might include oral clindamycin, trimethoprim-sulfamethoxazole, tetracyclines, or linezolid (level II evidence).\textsuperscript{65} Nonpurulent cellulitis is generally caused by \textit{Streptococcus} (group A, C, or G), while purulent cellulitis is substantially more likely to be caused by \textit{S aureus}, most commonly CA-MRSA.\textsuperscript{70-73} Treatment of nonpurulent cellulitis should therefore target streptococcal species with a \(\beta\)-lactam antibiotic, without routine addition of an agent active against MSSA or MRSA. Most, if not all, MRSA encountered by family physicians will be CA-MRSA, as it occurs primarily in the community context and is distinct from its highly drug-resistant relative, HA-MRSA (Table 2).\textsuperscript{65,74}

Complicated SSTIs and invasive MRSA infections, including bacteremia, septic arthritis, endocarditis, meningitis, and pneumonia, are typically treated with parenteral vancomycin (level I and III evidence).\textsuperscript{28,65} Susceptibility to clindamycin, trimethoprim-sulfamethoxazole, and tetracyclines is often retained in CA-MRSA isolates\textsuperscript{1-75} and these agents can be considered in nonsevere infection or as step-down therapy. These agents have good oral bioavailability.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{SSTI} & \textbf{TREATMENT*} \\
\hline
Simple cutaneous abscess (in a low-risk patient not involving face, hands, or genitalia) & Incision and drainage alone; obtain culture \\
\hline
Purulent cellulitis (without abscess); treat for CA-MRSA if risk factors present & Tetracycline, trimethoprim-sulfamethoxazole, or clindamycin \\
\hline
Nonpurulent cellulitis (no exudate); treat for \(\beta\)-hemolytic streptococcus & \(\beta\)-Lactam antibiotic (clavulanic acid or first-generation cephalosporin) \\
\hline
CA-MRSA–community-associated methicillin-resistant \textit{Staphylococcus aureus}, SSTI—skin and soft tissue infection. \\
\textsuperscript{*A detailed management algorithm is available within the Infectious Diseases Society of America guidelines 2014 update on SSTIs.\textsuperscript{65}} \\
\end{tabular}
\caption{Treatment of outpatient SSTI in the era of CA-MRSA}
\end{table}
Alternatives to vancomycin for the treatment of severe or invasive MRSA infection include linezolid, daptomycin, and tigecycline.5,28 Newer agents recently approved or developed that have shown promise are the cephalosporins ceftaroline and ceftobiprole; the lipoglycopeptides telavancin, dalbavancin, and oritavancin; and the oxazolidinone tedizolid.75-81 Pharmacologic and clinical considerations for each antimicrobial agent are listed in Table 3. Telavancin, oritavancin, and dalbavancin might be of particular interest to community-based health care services because of their once-daily, one-time, and weekly dosing, respectively (only dalbavancin is currently available in Canada).78-80 Table 4 provides a list of additional agents active against MRSA that are not available in Canada.

Failure of vancomycin therapy has been documented in the context of resistant strains (heterogeneous VISA, vancomycin-resistant *S aureus*), but these are unlikely

<table>
<thead>
<tr>
<th>Table 3. Antibiotics relevant in the treatment of MRSA</th>
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</thead>
<tbody>
<tr>
<td><strong>AGENT</strong></td>
</tr>
<tr>
<td><strong>Lincosamides</strong></td>
</tr>
<tr>
<td>• Clindamycin</td>
</tr>
<tr>
<td><strong>Sulfonamides</strong></td>
</tr>
<tr>
<td>• Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
</tr>
<tr>
<td>• Tetracycline</td>
</tr>
<tr>
<td>• Doxycycline</td>
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<tr>
<td>• Minocycline</td>
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<tr>
<td>• Tigecycline</td>
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<tr>
<td><strong>Oxazolidinones</strong></td>
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<tr>
<td>• Linezolid</td>
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<tr>
<td><strong>Lipopeptides</strong></td>
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<tr>
<td>• Daptomycin</td>
</tr>
<tr>
<td><strong>Lipoglycopeptides</strong></td>
</tr>
<tr>
<td>• Vancomycin</td>
</tr>
<tr>
<td>•Telavancin</td>
</tr>
</tbody>
</table>

ACEI—angiotensin-converting enzyme inhibitor, ARB—angiotensin receptor blocker, IV—intravenous, MRSA—methicillin-resistant *Staphylococcus aureus*, SSTI—skin and soft tissue infection.
The prevalence of CA-MRSA appears to be on the rise in crowded housing and homeless populations are disproportionately affected. Community-associated MRSA can be found in both hospitals and the community and is predominantly associated with purulent SSTIs.

Future research directions. This is an evolving science, and there is much to learn about community spread of CA-MRSA. As HA-MRSA primarily involves inpatients, it lends itself more easily to study. As CA-MRSA began entering the hospital setting it now lends itself to hospital-based research. While specific clinical questions around initial drug choice and duration remain, regional population studies are needed to inform empirical treatment for the community-based clinician.

Conclusion

The prevalence of CA-MRSA appears to be on the rise globally, and disadvantaged communities with overcrowded housing and homeless populations are disproportionately affected. Community-associated MRSA can be found in both hospitals and the community and is predominantly associated with purulent SSTIs.

Table 4. Additional agents active against MRSA not available in Canada

<table>
<thead>
<tr>
<th>AGENT</th>
<th>ROUTE</th>
<th>STATUS (AT TIME OF WRITING)</th>
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</thead>
<tbody>
<tr>
<td>Tedizolid</td>
<td>Oral or IV</td>
<td>Received NOC; not yet marketed</td>
</tr>
<tr>
<td>Ceftobiprole medocaril</td>
<td>IV</td>
<td>Received NOC; never marketed</td>
</tr>
<tr>
<td>Cefataroline</td>
<td>IV (weekly)</td>
<td>Not available</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>IV (1-time dose)</td>
<td>Not available</td>
</tr>
</tbody>
</table>


Treatment of endemic CA-MRSA infections needs to be balanced with the principles of antibiotic stewardship.

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Contributors

All authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

Competing interests

None declared

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References

Clinical Review


