Community-Acquired Methicillin-Resistant Staphylococcus aureus (CA-MRSA) Skin & Soft Tissue Infections (SSTI): Overview and Management

To address the growing problem of CA-MRSA SSTI within our health authority, the VIHA Antimicrobial Review Subcommittee (VIHA-ARS) of the Pharmacy and Therapeutics Committee has developed a treatment algorithm (see insert) to provide direction in managing these infections and to encourage a consistent treatment approach. This newsletter provides a brief overview of CA-MRSA and key points regarding treatment found in the algorithm.

Background

Methicillin-resistant Staphylococcus aureus (MRSA) has been a prominent pathogen, especially in hospitals and nursing homes, since the 1960s. The first case of MRSA reported in Canada was in 1981. Methicillin-resistant Staphylococcus aureus (MRSA) infections have until relatively recently been mostly nosocomial. The emergence of a new strain of MRSA causing predominantly (but not exclusively) community-acquired infections has changed that, resulting in a distinction between hospital-acquired (HA) and community-acquired (CA) strains. CA-MRSA infections have been observed globally, and were first noted in Canada in an Aboriginal population in Alberta from 1986 to 1989. CA-MRSA has since become an important pathogen implicated particularly in skin and soft tissue infection, but also in more severe disease including sepsis, necrotizing fasciitis, purpura fulminans, toxic shock syndrome, necrotizing pneumonia and empyema.

Genetic Distinction of CA-MRSA

As demonstrated in Figure 1, the nomenclature for the types of MRSA are not necessarily reflective of the source of acquisition. CA-MRSA and HA-MRSA are genetically distinct from each other and as such have different antimicrobial resistance profiles and are associated with different clinical syndromes. Both types of MRSA carry the mecA gene complex, which is carried on a specific integrative genetic element known as the staphylococcal cassette chromosome (SCC), and is responsible for beta-lactam resistance. There are five different SCCmec types (I through V); types I, II, and III are found predominantly in HA-MRSA isolates, whereas types IV and V are found in CA-MRSA isolates. This distinction accounts for the wider range of antimicrobials to which CA-MRSA are susceptible.

Key Points for Managing CA-MRSA SSTI:

- Systemic antibiotics are often unnecessary for localized disease with no systemic features.
- There are no clinical data to support combination therapy over monotherapy for treating CA-MRSA SSTI. Reserve combination therapy for severe infection.
- Rifampin should never be used on its own due to the potential for rapid development of resistance.
- Vancomycin dosing should be weight-based at 15 mg/kg, administered every 12 hours for patients with normal renal function (target trough before 3rd or 4th dose, 10-15 mg/L).
- If CA-MRSA suspected, always collect specimen(s) for culture and sensitivity.
Table 1 summarizes the typical antimicrobial susceptibilities and associated infections of CA-MRSA and HA-MRSA. In Canada, 10 strains of MRSA have been identified and labeled as CMRSA-1 (Canadian MRSA-1) to CMRSA-10 (Canadian MRSA-10). The dominant circulating strain of CA-MRSA in North America is CMRSA-10, which is equivalent to USA300.

Table 1. Comparison of associated clinical syndromes and typical antimicrobial susceptibilities of CA-MRSA and HA-MRSA in VIHA

<table>
<thead>
<tr>
<th>Associated clinical syndromes</th>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and soft tissue infections (furuncles, skin abscesses, cellulitis, folliculitis, impetigo, fasciitis, pyomyositis, wound infections), postinfluenza necrotizing pneumonia</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Nosocomial pneumonia, nosocomial- or catheter-related urinary tract infections, intravascular catheter or bloodstream infections, surgical-site infections</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

**Typical antimicrobial susceptibilities**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Linezolid</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Rifampin</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>V</td>
<td>R</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Macrolides</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

S = susceptible; R = resistant; V = variable; TMP/SMX = trimethoprim/sulfamethoxazole
Virulence Factors

CA-MRSA is distinguished also by the presence of certain virulence factors. Of these, a frequently occurring feature of CA-MRSA is the production of an exotoxin called Panton-Valentine Leukocidin (PVL), which produces tissue necrosis, mediated by cytokine release, and leucopenia (see Figure 2). This toxin may account for some of the hallmark presentations of CA-MRSA infections, including furunculosis and necrotizing pneumonia with a propensity to abscess formation. Based on this feature of CA-MRSA, it has been suggested that antimicrobial agents with the ability to inhibit exotoxin production (e.g. clindamycin and linezolid) may have an advantage. Currently, there is no clinical trial data to confirm or refute this hypothesis.

Risk Factors

Risk factors for CA-MRSA include intravenous drug use, prior antibiotic use, presence of underlying diseases such as diabetes mellitus, malignancy, and chronic skin disease, homelessness/shelter living, incarceration, aboriginal status, and origin from a known area/population with high rates of CA-MRSA. Populations in whom CA-MRSA cases have been concentrated include children (particularly those in day care centers), military recruits, incarcerated people, men who have sex with men, sports teams, and native populations. Sources of infection in community outbreaks of MRSA infection include close contact as well as shared contaminated objects such as athletic equipment, towels, and benches. It has also been hypothesized that cutaneous MRSA infection may be a sexually transmitted disease. It is important to note that CA-MRSA infections have affected a large number of people without the recognizable risk factors listed here.

Algorithm for the Treatment of CA-MRSA SSTI (see insert)

There are unfortunately few clinical outcome data pointing to the optimal treatment approach for CA-MRSA SSTI leaving many unanswered questions. The algorithm developed by the VIHA-ARS is based on published review literature, a consensus of local expert opinion, as well as local susceptibility patterns of CA-MRSA. Based on the best data that exist, a stepwise approach to the management of typical patients with suspected CA-MRSA SSTI is provided, according to degree of disease severity.

Most patients with mild infection (localized disease with no systemic features) can be managed as outpatients with abscess drainage and/or topical antibiotics alone. Patients with moderate infection (presence of multiple abscesses and/or cellulitis with minimal systemic features) can usually be treated with single agent oral antibiotic therapy. Antibiotic choices include trimethoprim/sulfamethoxazole (TMP/SMX), doxycycline, or clindamycin. If doxycycline or TMP/SMX are chosen, consideration should be given to the addition of a second agent (e.g. cephalaxin or penicillin V) for the coverage of Group A streptococcal infection if there is a high index of suspicion that this organism could be contributing to infection (e.g. rapid onset, lymphangitic streaking, regional lymphadenopathy). Some specialists favor routine combination therapy with rifampin in cases where susceptibility has been demonstrated, for a potential synergistic effect against staphylococcal species, although a consensus on this approach has not been established. It should be remembered that rifampin is a potent enzyme inducer of numerous cytochrome P450 (CYP450) enzymes, including 2B6, 2C8, 2C19, 2C9, 2D6, 3A4, 3A5, and 3A7, which can result in clinically important drug interactions. Also, rifampin should not be used as a single agent as resistance can develop rapidly. Because of limited evidence supporting the use combination therapy with rifampin, we recommend that rifampin be reserved for recurrent CA-MRSA infections.
Patients with severe infections usually require parenteral antibiotic therapy with vancomycin in addition to an oral agent active against CA-MRSA (e.g. TMP/SMX, doxycycline, or clindamycin). To ensure adequate concentrations at the site of infection, vancomycin should initially be dosed at 15 mg/kg, administered every 12 hours with normal renal function. Further dose adjustments should be made according to trough concentrations, drawn prior to the third or fourth dose (target 10-15 mg/L). As a protein synthesis inhibitor, clindamycin (administered parenterally) may have a role in decreasing bacterial toxin production and should be considered if the infection is considered life- or limb-threatening and/or the involvement of bacterial toxin production is suspected. The infectious diseases service or other appropriate specialty should be consulted promptly in the event of life- or limb-threatening infection.

The preceding paragraphs briefly describe the main points in the treatment of CA-MRSA SSTI as illustrated in the algorithm. The algorithm should be reviewed in detail for appreciation of the more subtle nuances in treatment approach. Finally, microbial surveillance is of utmost importance in the management of suspected CA-MRSA SSTI and obtaining quality specimens for culture and sensitivity for infections of all degrees of severity is recommended, even if the results are not anticipated to influence treatment decisions.

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Reviewed by: VIHA - Antimicrobial Review Subcommittee

References
Algorithm for treatment of CA-MRSA skin & soft tissue infection (SSTI)

Vancouver Island Health Authority

Suspected CA-MRSA SSTI
Decision based on epidemiology, clinical presentation, and risk factors (see reverse)

MILD
- Localized disease with no systemic features
- May include infected scratches, insect bites, furuncles, small abscesses, impetigo, or folliculitis
- Cellulitis NOT present

MANAGE AS OUTPATIENT
1. Drain abscess if present.
2. Culture fluid from abscess or purulent lesion.
3. If impetigo or folliculitis consider course of TOPICAL antibiotic (e.g. mupirocin 2% or fusidic acid 2%).
4. Systemic antibiotics are generally NOT required.

Await susceptibility results (48-72 hrs)

MRSA
- Is isolate susceptible to current antibiotic?
  - YES
    - Continue original antibiotic regimen.
  - NO
    - Change antibiotic(s) to a single PO agent optimally effective against MSSA (Table 3). Stepdown to PO treatment when appropriate (see stepdown criteria on reverse).

MSSA
- Change antibiotic(s) to a single IV agent optimally effective against MSSA (Table 3). Stepdown to PO treatment when appropriate (see stepdown criteria on reverse).

Clinical deterioration at 72 hours?
- NO
  - Continue with single agent
- YES
  - Reassess for presence of bacterial reservoir (e.g. tenosynovitis, bursitis, abscess). Consider imaging studies, drainage procedure, and/or adding second PO agent (Table 1).

Clinical improvement at 7 days?
- YES
  - Consult infectious diseases or other appropriate specialty and/or reasseess for presence of bacterial reservoir (e.g. tenosynovitis, bursitis, abscess). Consider imaging studies, drainage procedure, and/or adding second PO agent (if not already added; Table 1).
- NO
  - Consult infectious diseases or other appropriate specialty

MANAGE AS INPATIENT
1. Drain abscess if present.
2. Culture fluid from abscess or purulent lesions.
3. Begin course of empiric IV antibiotic(s) (Table 2) PLUS additional PO antibiotic (Table 1) (i.e. treatment will usually include IV vancomycin PLUS a PO agent effective against CA-MRSA +/- IV clindamycin).
4. For life- or limb-threatening infections, consult infectious diseases or other appropriate specialty immediately.

Await susceptibility results (48-72 hrs)

MRSA
- continuation of IV vancomycin + PO agent effective against CA-MRSA +/- IV clindamycin

MSSA
- Continue full treatment course (7-14 days). Stepdown to PO treatment when appropriate (see stepdown criteria on reverse).

Consult infectious diseases or other appropriate specialty

Clinical deterioration or no improvement at 72 hours?
- NO
  - Continue full treatment course.
- YES
  - Consult infectious diseases or other appropriate specialty

ABBREVIATIONS
CA = community acquired
ED = Emergency Department
MRSA = methicillin-resistant Staphylococcus aureus
MSSA = methicillin-sensitive Staphylococcus aureus
OPAT = outpatient antimicrobial therapy
Algorithm for treatment of CA-MRSA skin & soft tissue infection (SSTI)
Vancouver Island Health Authority

NOTE: This algorithm is to be used as a guide for decision-making with respect to the treatment of presumed CA-MRSA skin and soft tissue infections only. An appropriate treatment pathway for other types of CA-MRSA infections is beyond the scope of this algorithm.