



Methicillin-Resistant *Staphylococcus aureus*: An Update

Staphylococci are responsible for a plethora of infections, including cellulitis, boils, skin abscesses, surgical site infections, endocarditis, osteomyelitis and bacteraemia. An increasing number of staphylococcal infections are related to medical developments, including the use of joint prostheses, immunosuppressants and longer-term intravenous catheters. Methicillin, a semi synthetic penicillin, was introduced in 1961 to deal with the problem of penicillin-resistant *S. aureus* in hospitals. Unfortunately, methicillin resistance in *S. aureus* (MRSA) was detected soon after the drug was introduced and, apart from a period during the early 1970s, the incidence of MRSA has steadily increased. MRSA associated with healthcare has posed a major problem with the first reported outbreak in Canada occurring in Toronto in the early 1980s (1). The recent rapid rise of community-associated MRSA (CA-MRSA) has further added to the burden of MRSA infections. Thus, attention has been increasingly focused on the severity and frequency of infections caused by MRSA, and its greater clinical and economic impact compared to methicillin-susceptible *S. aureus* (MSSA). This review provides updated information regarding the prevalence of MRSA in Canada and highlights some of the new information provided in the most recent Infectious Diseases Society of America (IDSA) clinical practice guidelines for the treatment of MRSA infections (2).

Are community associated MRSA (CA-MRSA) and hospital associated MRSA (HA-MRSA) different?

Since CA-MRSA hadn't yet been recognized as a separate entity, early studies examining the emergence and prevalence of MRSA were focused in the hospital setting. However, surveillance studies carried out during the last decade have distinguished between the two, either by their different genetic characteristics or whether or not the patient had or had not been exposed to a healthcare setting.

HA-MRSA strains are usually multi-resistant to non-beta-lactam antibiotics and contain staphylococcal cassette chromosome mec (SCCmec) type I, II, or III. In contrast, CA-MRSA strains were originally susceptible to most anti-staphylococcal antimicrobials, usually carry the smaller mec cassettes of type IV or V, and often have distinct genetic determinants of virulence, including Panton-Valentine leukocidin (PVL), a cytotoxin that causes white blood cell destruction.

Although these characteristics initially distinguished HA-MRSA from CA-MRSA,

there is an increased blurring of the two categories as CA-MRSA has moved into the health care setting, and is becoming resistant to other antibiotics.

What is happening with HA-MRSA and CA-MRSA in Canada?

The majority of MRSA infections and colonizations in Canada continue to be associated with exposure to some form of health care. There are a number of surveillance systems which have produced data on MRSA in Canada in recent years.

CANWARD, a cross-Canada surveillance program that consists of 15 sentinel hospitals in 8 provinces, monitors antimicrobial susceptibility of clinical isolates obtained from patients in clinics, emergency departments, medical and surgical wards and intensive care units. In data collected from blood, wounds, urine and the respiratory tract in 2009, *S. aureus* was the most commonly isolated organism and the second most common isolate from blood cultures. Overall, 21% of *S. aureus*, and 20% of *S. aureus* from blood cultures were HA-MRSA. (Figure 1)

Spider Bite



MRSA



Images courtesy of Scott Camazine

The Canadian Nosocomial Infection Surveillance System (CNISP) has monitored MRSA rates since 1995. Forty-seven sentinel hospitals from nine Canadian provinces submit data on all hospitalized patients with MRSA. There has been a steady increase in MRSA rates across the country. CNISP reported an increase in MRSA (combined colonization and infection) from 0.65 cases/10,000 patient-days in 1995 to 12.4 cases/10,000 patient-days in 2009. Hospital-acquired MRSA account for nearly two-thirds of all cases (8 cases/10,000 patient-days in 2009) (Figure 2) (3), but community acquired MRSA have increased over the past 5 years: in 2009, almost a third of new cases of MRSA did not have recent healthcare exposure.

In Ontario, The Quality Management Program-Laboratory Services (QMP-LS) has been tracking emerging resistance in hospital pathogens since 1996. In 2010, 21,002 patients were identified as colonized or infected with MRSA in Ontario, an 8% increase over the previous year. The percentage of patients infected (as opposed to colonized) with MRSA was 33%. Laboratories were

unable to determine a possible source of the MRSA in 55% of patients. Of the remainder, 41% of MRSA was thought to be acquired in hospitals, 17% in nursing homes and 42% in the community.

CA-MRSA was first observed in marginalized populations in the US and, in general, under conditions of close physical contact, overcrowding and poor hygiene. In Canada outbreaks of CA-MRSA have been described in at-risk populations, but there have also been many reports of MRSA infection in individuals without risk factors (4).

In Canada, the rise of CA-MRSA is primarily due to the epidemic strain Canadian MRSA-10 (CA-MRSA) (the same strain is called USA300 in the United States). Between 2007 and 2009, CANWARD assessed the demographics, antimicrobial susceptibility, and molecular epidemiology of CA-MRSA and HA-MRSA in Canadian hospitals. Among 3589 *S. aureus*, 24.8% were MRSA; 224 (25.2%) of these were CA-MRSA genotypes and 72.4% were HA-MRSA genotypes. The prevalence of CA-MRSA genotypes increased from 19.5% in 2007 to 31.9% in 2009 ($P < .001$)(5).

When should treatment for CA-MRSA be initiated?

The emergence of CA-MRSA has resulted in increases in emergency room visits and hospital admissions for skin and soft tissue infections (SSTIs) (6,7). Adam *et al.* surveyed patients with *S. aureus* SSTIs who presented to Toronto emergency departments between March 1st and June 30th, 2007(8). MRSA was isolated from 58 (19%) of 299 eligible patients. CMRSA-10 was identified at 6 of the 7 study sites and accounted for 50% of all cases of MRSA. Individuals with CMRSA-10 were younger (median 34 v. 63 yr, $p = 0.002$), less likely to report recent antibiotic use (22% v. 67%, $p = 0.046$) or health care-related risk factors (33% v. 72%, $p = 0.097$) and more likely to report community related risk factors (56% v. 6%, $p = 0.008$) than patients with other MRSA strains.

The Infectious Diseases Society of America (IDSA) has issued treatment guidelines for MRSA in order to help clinicians choose the best treatments for patients infected with both hospital and community associated MRSA. The primary objective of these guidelines is to provide recommendations on the management of some of the most common clinical syndromes, infections of skin and soft tissue, along with rarer but more serious problems such as blood infections, endocarditis, pneumonia, bone and joint infections. These recommendations are based on the prevalence of HA-MRSA and CA-MRSA reported in the US; Canadian clinicians should interpret these guidelines based on their local experience with MRSA prevalence. Recently published Canadian Anti-infective

Guidelines for Community-acquired Infections recommend that empiric coverage for MRSA should be considered in areas where MRSA is commonly isolated (>10-15% of *S. aureus*) or in patients with prior antibiotic use or hospitalization in the previous 6-12 months.

When CA-MRSA infection is suspected, refer to IDSA guidelines for treatment of specific infectious syndromes (2).

What antibiotics can be used to treat MRSA ?

Simple abscesses or boils can be managed with incision and drainage alone. Antibiotics do not appear to improve outcomes. However, antibiotic therapy is recommended for abscesses associated with severe or extensive disease (eg, multiple sites or rapid progression with associated cellulitis), at sites difficult to drain completely or that do not respond to incision and drainage, when patients have signs and symptoms of systemic illness or septic phlebitis, or for patients who are frail, immunosuppressed or at the extremes of age. Oral antibiotics that may be used as empiric therapy for CA-MRSA following incision and drainage of abscesses include trimethoprim-sulfamethoxazole (TMP-SMX), doxycycline (or minocycline), clindamycin and linezolid. Rifampin is not recommended alone or in combination due to risk of emergence of resistance.

In areas where there is a high prevalence of MRSA, outpatients with purulent cellulitis may be treated empirically for 5-10 days pending culture results. For erysipelas and non-purulent cellulitis, empiric therapy for beta-haemolytic streptococci is recommended.

For hospitalized patients with complicated SSTI, bacteraemia, pneumonia, endocarditis, CNS infection, bone and joint infections and device related infections, IV therapy with vancomycin (alone or in combination) is the preferred antibiotic choice. IV daptomycin, linezolid or clindamycin are alternatives for complicated skin and soft tissue infections, or bone and joint infections. Linezolid and clindamycin are alternate therapies for treatment of pneumonia, linezolid or TMP-SMX for CNS infections, and daptomycin for bacteraemia or native valve endocarditis.

Detailed treatment recommendations published in the IDSA Clinical Practice Guideline are available at <http://cid.oxfordjournals.org/content/early/2011/01/04/cid.ciq146.full.pdf+html>

Is there a concern about patients failing treatment with vancomycin?

Clinical or microbiological failures occur in a substantial proportion of invasive MRSA

infections treated with vancomycin. Persistent bacteraemia is associated with worse clinical outcomes. Vancomycin treatment failures have been attributed to the drug's slow bactericidal activity, emergence of strains with reduced susceptibility to vancomycin, possible enhanced virulence of CA-MRSA, and inadequate debridement or an unremoved/undrained focus of infection (eg. retained prosthetic device). At this time, no alternative agent or regimen has proven to be superior to vancomycin in achieving clinical cure or sterilizing blood cultures. Because the median time to clearance of MRSA bacteraemia is 7-9 days, most experts agree that persistent bacteraemia at or around day 7 of therapy should prompt an assessment to determine whether a change in therapy is indicated. The threshold to reassess and change therapy may be earlier if the patient's clinical condition is worsening despite adequate debridement and removal of other foci of infection or if the MRSA isolate's vancomycin MIC is 2 µg/mL, particularly in septic or critically ill patients. The IDSA Panel recommended a change in therapy rather than the addition of other agents to vancomycin.

How should results of vancomycin susceptibility testing be used to guide therapy?

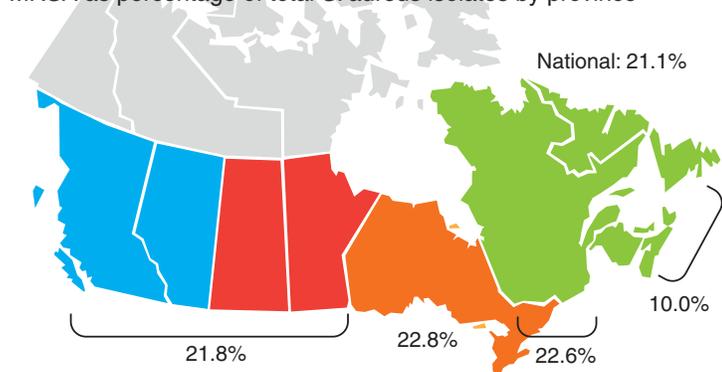
The emergence of intermediate and resistant *Staphylococcus aureus* (VISA and VRSA) as well as hVISA (the stage that preceded development of intermediate resistance) poses an additional challenge to use of vancomycin. Although such isolates are relatively uncommon (10), they are associated with vancomycin treatment failures and poor outcomes. As well, concern has been raised that "MIC creep" is occurring, that is, that MRSA are slowing becoming less susceptible to vancomycin.

This prompted, the US Clinical Laboratory Standards Institute (CLSI) to lower the MIC breakpoint for susceptible strains from ≤4µg/mL to ≤2µg/mL, with MICs of 4-8 µg/mL and ≥16 µg/mL now indicating intermediate and resistant strains, respectively. In January 2011, the European Commission Antimicrobial Susceptibility Testing (EUCAST) published a revised edition of clinical breakpoints for vancomycin susceptible strains, the MIC is ≤2 mg/L and resistant is > 2 mg/L. It was noted that *S. aureus* with vancomycin MIC values of 2 mg/L are on the border of the wild type MIC distribution and there may be an impaired clinical response in infections due to such strains. The resistant breakpoint has been reduced to 2 mg/L to avoid reporting glycopeptide intermediate *Staphylococcus aureus* (GISA) isolates as intermediate, since serious infections with GISA are not treatable with any dose of vancomycin or teicoplanin. (11)

Figure 1. MRSA as percentage of total *S. aureus* isolates by province

CANWARD 2009 HA-MRSA & CA-MRSA

MRSA as percentage of total *S. aureus* isolates by province



*MRSA/Total *S. aureus* (232/1 102) = 21.1%

Zhanell et al. Results from the National CANWARD Study 2009. www.can-r.ca

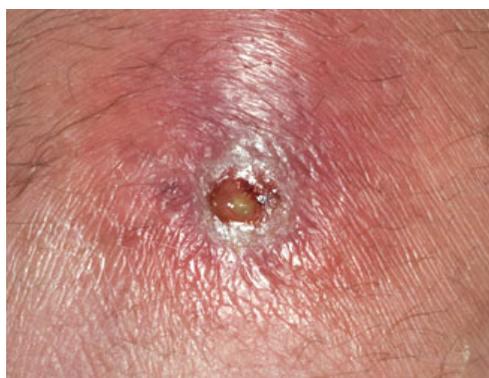
Unfortunately, laboratory detection of strains with reduced susceptibility to vancomycin—in particular, hVISA, in which a small, resistant subpopulation of cells is present—remains difficult or impossible. Several tests, including the microdilution Etest, Etest glycopeptide resistance detection, and Mueller-Hinton agar with 5 mg/L teicoplanin have been proposed, but which assay best predicts whether a patient will respond to therapy remains unclear. Because of this limitation, testing for hVISA is not routinely recommended in Canadian laboratories.

Interpretation of vancomycin MICs is further complicated by the considerable variability in MIC results, depending on which method is used and the acceptable variability for MIC methods is +/- 1 doubling dilution, which makes it difficult to distinguish between an MIC of 1 µg/mL versus 2 µg/mL. The automated systems used by most laboratories have biases. MicroScan, and BD-Phoenix report MIC values that are higher than those reported by reference broth microdilution, resulting in susceptible strains being labelled as intermediate in some cases. In contrast, the Sensititre and Vitek 2 systems tend to under call resistance and may miss intermediate strains.

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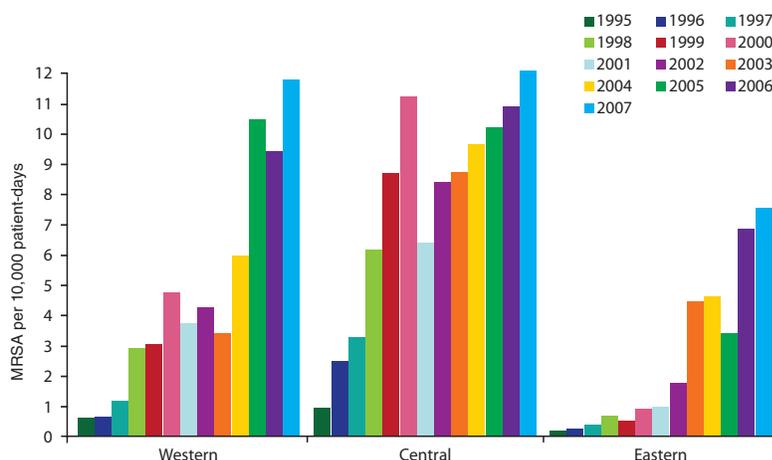
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These laboratory challenges have meant that the IDSA MRSA guidelines recommend that, for isolates with a vancomycin MIC of ≤2 µg/mL, the patient's clinical response should determine the continued use of vancomycin, independent of the MIC. If the patient has had a clinical and microbiological response to vancomycin, then it may be continued with close follow-up. If the patient has not had a clinical or microbiological response to vancomycin despite adequate debridement and removal of other foci of infection, an alternative to vancomycin is recommended regardless of MIC.



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Figure 2. Overall Canadian MRSA incidence rates per 10,000 patient days by region from 1995 to 2007 (Ref 11).



Carbapenem-resistant Enterobacteriaceae (CRE) – A Primer

Carbapenems are β-lactam antibiotics used to treat antibiotic-resistant infections caused by gram-negative bacteria. Over the last decade, a number of carbapenemases – β-lactamases that are active not only against penicillins and cephalosporins but also carbapenems – have evolved. These enzymes are usually located on a mobile genetic element (eg. plasmid, transposon, or integron). They are most commonly found in Enterobacteriaceae, but also occur in *Pseudomonas aeruginosa* and *Acinetobacter*. Although new carbapenemases evolve rarely, they spread easily, as do the bacteria carrying them, and outbreaks have been reported in healthcare systems worldwide. Because they evolve under antibiotic pressure, most bacteria producing carbapenemases are resistant not only to β-lactams, but also to other classes of antibiotics including fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole. Often, the only antibiotics that carbapenemase-producing bacteria are susceptible to are colistin and tigecycline.

The most common types of carbapenemases are called KPC, NDM, VIM and OXA. KPC (*Klebsiella pneumoniae* carbapenemase) is most prevalent in hospitals on the US Eastern seaboard (1-3), Israel (4) and Greece (5). However, transmission of bacteria carrying KPC has been reported from hospitals around the world, and several outbreaks have been reported in Ontario hospitals (6-8). Although KPC is most common in *Klebsiella pneumoniae*, plasmid spread has occurred to other Enterobacteriaceae, and both clonal and plasmid outbreaks have been described. (9,10)

New Delhi metallo-β-lactamase (NDM) producing plasmids are widespread in Enterobacteriaceae in hospitals and in the community in the Indian subcontinent (11). Many countries have reported cases imported

from the Indian subcontinent, and transmission has been described in a number of countries (12-13). To date, more than 20 patients with NDM-producing bacteria have been identified in Ontario hospitals, including cases acquired in Ontario (14). Most outbreaks involve multiple bacterial species: spread of the plasmids containing NDM is very common.

VIM (Verona integron encoded metallo-β-lactamase) producing bacteria have been reported most commonly from Greece, and the eastern Pacific rim (eg. Japan, Taiwan, China). Outbreaks have been described not only in Enterobacteriaceae, but also *Pseudomonas aeruginosa*, and *Acinetobacter*. OXA producing bacteria have most commonly been reported from France and Turkey, and pose challenges because they are particularly difficult to detect in the laboratory.

Because CRE are resistant to all penicillins, cephalosporins, carbapenems and other classes of antimicrobials, treatment of infections with CRE is difficult and involves the use of antibiotics that are associated with significant rates of serious adverse events (e.g., colistin, chloramphenicol). Several studies have identified that infections due to carbapenemase producing organisms have significantly worse outcomes than those due to ESBL-producing bacteria despite aggressive therapy (15). The case fatality rate for serious infections may be as high as 50% (16). Recent data regarding the pharmacokinetics of colistin suggest that the appropriate breakpoint

for susceptibility to colistin is 1ug/ml - in other words, many CRE isolates that are now reported as susceptible to colistin are, in fact, resistant (17).

In Canada, the major risk factor for CRE is receipt of care in health care facilities with endemic or epidemic CRE. This includes hospitals along the U.S. eastern seaboard, particularly New York City (KPC), Greece (KPC or VIM), Israel (KPC) and the Indian subcontinent (NDM-1). However, CRE outbreaks are being increasingly described in hospitals around the world, including Canada.

The rapid emergence of carbapenemases mean that Canadian laboratories should be screening all isolates of Enterobacteriaceae for their presence. In clinical isolates, MIC values to ertapenem and/or meropenem should be determined (18). The Clinical Laboratory Standards Institute has recently published new screening breakpoints (≤ 0.25 µg/ml for ertapenem and ≤ 1 µg/ml for meropenem); isolates that are intermediate or resistant by these breakpoints should be suspected of harboring a carbapenemase and further tested by phenotypic inhibitor testing (19) or PCR, or submitted to a reference laboratory for confirmation.

Infection control recommendations require that laboratories be able to screen at-risk patients for colonization with CRE (18,20,21). Rectal swabs are the specimen recommended for this screening, although stool specimens are

also acceptable. No carbapenem-containing selective medium reliably detects all the different types of CRE. Thus to reliably detect CRE, screening specimens, should be planted onto selective media for ESBL-producing Enterobacteriaceae (avoid chromogenic ESBL agars because they may inhibit CRE that also produce ampC). Any Enterobacteriaceae growing on the ESBL screening media should have meropenem disc diffusion testing on Mueller-Hinton agar; isolates that have zones ≤ 25 mm (EUCAST epidemiologic cut-off for *E. coli*) should be further investigated using a phenotypic inhibitor method (e.g., Rosco diagnostic tablets KCP+MBL Confirm kit Pro-Lab) and/or molecular testing for carbapenemases.

Patients colonized or infected with CRE should be managed with additional precautions that include: a private room, use of contact precautions by those entering the room, additional cleaning of the environment and equipment, and dedication of all mobile equipment to the patient for their length of stay. (18,20,21) Control of transmission of CRE requires stringent adherence to precautions and cleaning, and management of outbreaks has often required both geographic and staff cohorting (22).

In sum, CRE will pose significant challenges to microbiology laboratories, infection control programs, and infectious disease specialists in Canada over the next few years. Coordinated efforts to optimize prevention will be needed to best protect patients.

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