EDITORIAL

Over the past 2 decades, methicillin-resistant Staphylococcus aureus (MRSA) has become a major public health concern. Today, MRSA not only has one of the most extensive resistance profiles to antibiotics – being resistant to all beta-lactam antibiotics except the novel cephalosporins - it is also infamous for being the pathogen that has had the most significant impact on the media and on the general public’s awareness of the issue of antibiotic resistance.

First emerging as a major pathogen in healthcare institutions in the early 1960s, the epidemiology of MRSA infections began to change in the late 90s, due to the emergence of community-associated MRSA (CA-MRSA). Genetically quite distinct from healthcare-associated MRSA (HA-MRSA), CA-MRSA predominantly causes skin and soft tissue infections (SSTI). As a result of the emergence of CA-MRSA, the number of outpatient visits and hospitalizations for SSTIs has dramatically increased in recent years. And whereas HA-MRSA primarily affects the elderly population and individuals with co-morbidities, CA-MRSA peaks in healthy children, adolescents and 30-40 year olds. Furthermore, in some countries (e.g. in Greece, the US and Taiwan), CA-MRSA strains are becoming increasingly frequent in hospitals, where they are now the cause of healthcare-associated infections (HAI). The changing epidemiology of MRSA in general has necessitated a change in the treatment of such infections.

The feature article in this issue focuses on the epidemiology of CA-MRSA, the impact of its appearance in the healthcare setting, and future perspectives for containment.

This article is complemented by a summary of the recent IDSA Guidelines for the treatment of MRSA infections. The review focuses on SSTI, bacteremia, and pneumonia in adults, together with recommendations relevant to the microbiology laboratory.

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STATE-OF-THE-ART

CA-MRSA – Epidemiology and perspectives

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Staphylococcus aureus, and more specifically methicillin-resistant S. aureus (MRSA), is one of the most important bacterial pathogens in the world. MRSA isolates are resistant to all beta-lactam antibiotics except ceftriaxone, a novel cephalosporin with anti-MRSA activity thus rendering them resistant to the most potent anti-staphylococcal antibiotics. Resistance is due to the mecA gene situated in a cassette named Staphylococcal cassette chromosome mec (SCCmec).

MRSA was first described in the UK in 1961. The strain belonged to clonal complex (CC) 8 carrying SCCmec type I and has been named the archaic clone. This clone spread widely in some countries in Europe, i.e. Denmark, France, Switzerland and the UK but also in Australia during the 1960s, whereas it did not spread in the US. This clone largely disappeared in the 1970s.

Beginning in the late 1970s, a second wave of MRSA spread in hospitals in the US and in the rest of the world resulting in MRSA being hyper-endemic throughout the world in the 1990s. More than 90% of the MRSA infections were caused by isolates belonging to only 5 lineages [CC5, CC8, CC22, CC30 (ST36) and CC45] carrying SCCmec I-VI(1).
In the late 1990s, the epidemiology of MRSA infections began to change. Increasingly, MRSA caused infections in persons without any connection to healthcare institutions i.e. community-associated MRSA (CA-MRSA). This paper will focus on the epidemiology of CA-MRSA. The paper will also look at the possible perspectives for future containment of MRSA.

**DEFINITION OF CA-MRSA**

Defining CA-MRSA is not an easy task. This is due to several issues; firstly, the fact that persons can carry *S. aureus* for prolonged time periods without having symptoms, makes it difficult to determine the exact time and place of the acquisition in most cases. A definition that includes both epidemiological data (especially contact with the healthcare system) and microbiological data (especially typing) is best, but these data are often not available (2). This has lead to a number of surrogate markers including SCCmec type IV and V, non multiresistance and ciprofloxacin susceptibility and a positive test for Panton Valentine Leukocidin (PVL) virulence factor (3). However, none of these surrogate makers are suitable for CA-MRSA screening, as each of them may be missing or be found in typical HA-MRSA strains as well.

**HISTORY OF CA-MRSA**

Although CA-MRSA was not recognized as a separate entity and did not spread widely until the late 1990s, CA-MRSA cases have been described as early as 1982, where cases were seen among drug addicts in the US (4). In 1993, Udo and co-workers reported the endemic presence of CA-MRSA in aboriginal communities in Western Australia dating back to the start of the 80s (ST8-MRSA-IV /WA MRSA 5) (5), and in New Zealand, CA-MRSA was reported in 1996 (ST30 - IV) (6).

In 1998, Herold et al reported a significant increase in the number of MRSA among non-hospitalized children in the Chicago area (7), although at that time it was perceived as an oddity (8). Later, a number of retrospective studies identified sporadic cases of CA-MRSA throughout Europe. The report of the death of 4 children in MMWR in 1999 changed the perception of CA-MRSA from being an oddity to being recognised as a separate entity that must be taken seriously (9).

**MICROBIOLOGY OF CA-MRSA**

Microbiologically speaking, CA-MRSA is also a separate entity. Like HA-MRSA, there are still relatively few lineages that are found worldwide, but the number of new CA-MRSA strains is rapidly growing. Currently, the dominating CA-MRSA lineages include ST1-IV (USA400); ST8-IV (USA300); ST30-IV (Pacific/Oceania); ST59-IV and V (USA1000, Taiwan); ST80-IV (European CA-MRSA strain) (10). Common to all these lineages is the fact that they carry the relatively small SCCmec I cassettes have less fitness than strains with SCCmec IV cassettes (11).
**Clinical Picture of CA-MRSA**

As CA-MRSA predominantly affects otherwise healthy people, the clinical picture of CA-MRSA is quite different from what is seen in HA-MRSA where the type of infections often reflects underlying diseases, use of IV-catheters (i.e. bacteremia) and surgery (i.e. post-operative wound infections). CA-MRSA are dominated by skin and soft tissue infections including abscesses as illustrated by data from the Danish notification system (Figure 2). Likewise, there are major differences in who is affected. HA-MRSA cases reflect the age distribution of hospitalized patients with the far majority of cases being in the elderly. In contrast, CA-MRSA peaks in children and adolescents and again among 30-40 year old persons (Figure 3). As close contact, especially within families, is the predominant route of transmission, the peak among the 30-40 year olds most likely reflects transmission from children to their parents. It should, however, be noted that when CA-MRSA strains are introduced into hospitals, it results in clinical pictures that are indistinguishable from those caused by HA-MRSA strains.

Spread of MRSA in “closed communities” is favoured by the 5C’s (Table 2) often combined with frequent antibiotic use / overuse (12).

**Table 1**

<table>
<thead>
<tr>
<th>Traditional risk factors for nosocomial MRSA infection</th>
<th>Risk factors for community acquired (CA) MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Previous hospital stay</td>
<td>- History of colonization/infection with CA-MRSA</td>
</tr>
<tr>
<td>- Prolonged length of stay prior to infection</td>
<td>- Close contact with a person colonized/infected with CA-MRSA</td>
</tr>
<tr>
<td>- Surgical procedure(s)</td>
<td>- Adults ≥65 years; children &lt;2 years</td>
</tr>
<tr>
<td>- Enteral feeding</td>
<td>- Indigenous people</td>
</tr>
<tr>
<td>- Previous antibiotic use</td>
<td>- “Special communities”</td>
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<tr>
<td>- Central venous catheter insertion</td>
<td>Participation in contact sports</td>
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<td></td>
<td>Injection drug use</td>
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<tr>
<td></td>
<td>Living in correctional facilities or shelters</td>
</tr>
<tr>
<td></td>
<td>Military personnel</td>
</tr>
<tr>
<td></td>
<td>Men who have sex with men</td>
</tr>
</tbody>
</table>

The problem with MRSA spreading in these closed communities is that MRSA is amplified and is likely to disseminate from these communities into the population in general.

**Table 2**

- Poor hygiene / Cleanliness
- Compromised skin
- Frequent skin contact
- Contaminated surfaces and shared items
- Crowding (up to 7.5 persons per bedroom)

**Risk Factors for CA-MRSA**

The risk factors for acquiring CA-MRSA also differ from HA-MRSA (Table 1). A history of colonization/infection with CA-MRSA or close contact with a person colonized/infected with CA-MRSA are the most important risk factors for acquisition of CA-MRSA. In addition, a number of risk situations have been described, especially in the US, including participation in contact sports, injection drug abusers, living in correctional facilities or shelters, military personnel and men who have sex with men, but these are rare risk factors in Europe. Moreover, MRSA have been shown to be highly prevalent among indigenous people in Australia, Canada, the Pacific Islands and the US (15).

**CA-MRSA CARRIAGE IN THE GENERAL POPULATION**

It has been argued that CA-MRSA, which most often causes relatively mild diseases that can be cured by incision or oral antibiotics, is more a nuisance than a real problem. The problem with CA-MRSA is, however, its ability to survive and spread in the community, leading to an increasing number of colonized persons in the general population. Carriage rates among the general population are still low in most places including Europe (<1%). In the US, 1.5% were positive in the latest NHANES survey in 2003-4, however, this figure had doubled from 0.8% in 2000-1 (13). Far larger carriage rates of MRSA - as high as 10% - have been shown in Mexico and Taiwan (14, 15). Increasing carriage among the general population may, or more probably will, lead to the increased introduction of CA-MRSA into hospitals – carried by persons without any known risk factors for MRSA. Mathematical models that take spread in the community into account have shown that this has significant influence, not only on MRSA infections in the community, but also on the incidence of healthcare-associated MRSA infections (16, 17). In fact, the number of patients who need to be isolated in hospitals to control MRSA transmission was 6-7 times higher and the effect of the interventions only slowly reduced the prevalence of MRSA when simulations included transmission in the community, compared to when community transmission was negligible (17).
CA-MRSA AS A CAUSE OF HEALTHCARE-ASSOCIATED INFECTIONS (HAI)

In most countries, MRSA HAI is still predominantly caused by traditional HA-MRSA. However, the epidemiology of MRSA is becoming increasingly blurred with CA-MRSA now causing HAI, and at significant levels in some countries. In Greece, 25% of HA-MRSA infections are caused by the ST8-VI strain (European CA-MRSA clone) (18). In the US, there has been a dramatic change in epidemiology, and CA-MRSA strains, especially ST8-IV (USA300), are now very frequent in many US hospitals where, to some degree, they have displaced HA-MRSA strains (19, 20, 21). Taiwan is a third example of this, where ST59-VI causes 13% of HA-MRSA and 47% of MRSA HA-MRSA strains (19, 20, 21).

Furthermore, the increasing prevalence of CA-MRSA leads to MRSA bacteremia with community onset becoming increasingly frequent. For example, in a recent large multicentre investigation from Australia and New Zealand, 61% of Staphylococcus aureus bacteremia (SAB) cases were community onset with 18% being MRSA, and 27% of all MRSA cases had an antimicrobial susceptibility profile typical for CA-MRSA strains (22). Similarly, in a French multicentre study of invasive MRSA clones in France, 39.7% had community onset, and in a study from a Taiwanese emergency department, 24% of MRSA bacteremia patients did not have healthcare-associated risk factors (23, 24).

Community-onset MRSA bacteremia is an important issue for clinicians as coverage of MRSA by the initial antibiotic treatment has significant impact on patient survival (25). However, it has also been shown that vancomycin treatment of MRSA is associated with significantly poorer outcome compared to treatment using β-lactam antibiotics. Increasing prevalence of community-onset MRSA bacteremia may also necessitate treatment with both drug classes – leading to excessive use - and thereby drive resistance in other organisms such as enterococci.

CONTAINMENT OF CA-MRSA

Can CA-MRSA be contained? Recent evidence both from The Netherlands and Denmark shows that persons can be successfully decolonized and transmission chains can thus be stopped (26). Tinna Uth, Ulla Hjort, Mette Sgaard, Robert Skov: Successful control of CA-MRSA in Denmark: Mission impossible? Poster at the 3rd HAI Forum, June 27-30, 2011, Anncy, France). However, mupirocin and chlorhexidine need to be used cautiously as there is risk of development of resistance. Resistance towards mupirocin is well known if applied to larger groups of patients i.e. in a hemodialysis unit. Recently, data from Geneva have shown that this can also be seen if used extensively for decolisation of MRSA carriage (27). On the contrary, mupirocin resistance is very low in Denmark, even though almost all CA-MRSA patients are offered treatment.

In order to avoid development of resistance, it is important not to start treatment as long as there are risk factors present such as IV-lines, indwelling catheters, ulcers or ongoing infections. As there is often more than one positive person in a household, it is important that the whole household / all MRSA positive persons in a household are treated simultaneously. In the case of throat carriage, it will often be necessary to repeat topical treatment, and in 30-40% of cases, addition of systemic treatment is necessary. Even though the success rate for decolisation is very high, both in The Netherlands and Denmark, both countries are experiencing an increasing incidence of CA-MRSA. At least for Denmark, this is due to a very high influx of CA-MRSA in connection with travel abroad or visits of family from foreign countries, whereas transmission in Denmark outside families is modest – perhaps due to the extensive use of decolisation treatment.

IN CONCLUSION

CA-MRSA is increasing throughout the world. This results in an immediate increase in burden of disease, but far more seriously leads to increasing prevalence of MRSA carriers in the general population who can carry MRSA into hospitals where it may develop into an infection, but also occasionally be transmitted to other patients, thereby increasing the burden of HAI. CA-MRSA is thus a matter of concern and infection control measures should be taken to help prevent further spread in order to contain CA-MRSA.
The increased prevalence of methicillin-resistant Staphylococcus aureus (MRSA) has been a major concern within the healthcare community over the past 15 years. Though this pathogen had historically been limited to healthcare institutions, MRSA has now become a major cause of community-associated infections, particularly skin infections. The emergence of community-acquired MRSA, which is genetically distinct from hospital-associated MRSA, has changed the epidemiology of this pathogen and necessitated a change in the empirical therapy of such infections.

In January, 2011 the Infectious Diseases Society of America (IDSA) released their first guideline for management of MRSA infections (available at www.idsoc.org). The guidelines appeared in the February 2011 issue of Clinical Infectious Diseases. The stated purpose of the MRSA treatment guidelines was to provide recommendations on the management of the most common clinical syndromes encountered in both adult and pediatric patients with MRSA infection.

For this review I will focus on skin and soft tissue infections, bacteremia, and pneumonia in adults as well as the recommendations relevant to the laboratory for this very important pathogen. The following are selected recommendations from this new guideline (specific recommendations are graded as to the strength of recommendation A being strongest, and the level of evidence with I being the highest). The reader is referred to the guideline for recommendations for other infections (such as bone and joint and CNS infections) and for specific pediatric issues.

For hospitalized patients with complicated SSTI (defined as patients with deeper soft-tissue infections, surgical/traumatic wound infection, major abscesses, cellulitis, and infected ulcers and burns), in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered pending culture data.

As the authors of the guideline acknowledge, the benefit of antibiotics in addition to incision and drainage for simple abscess is controversial. Additional prospective, large-scale studies that are currently underway will provide more-definitive answers to this question. Antimicrobial options for outpatients as listed in the guideline include trimethoprim/ sulfamethoxazole, doxycycline, minocycline, clindamycin and linezolid. The guideline also indicates that while linezolid is FDA-approved for skin infections it has not been shown to be superior to less expensive alternatives in the treatment of these mild infections.

Some interesting potential drugs included in the But this guideline did not include the following considerations: Ceftaroline was not FDA approved at the time of the writing of this guideline, but the guideline recognized this cephalosporin as a potential option pending approval. Recurrent staphylococcal furunculosis is common and a frustrating condition for patients. This guideline suggests that most experts define “recurrent disease” as 2 or more discrete infections at different sites within a 6 month period. The approach to this is controversial and there are subsequently many different strategies that have been suggested. The guideline suggests a multifaceted approach that actively engages the patient in personal and environmental hygiene measures applicable to the household or community setting while also focusing on strategies for decolonization. Decolonization may be considered in selected cases if:

- A patient develops a recurrent SSTI despite optimizing wound care and hygiene measures (C-III); or ongoing transmission is occurring among household members or other close contacts despite optimizing wound care and hygiene measures (C-III).
Decolonization strategies include nasal decolonization with mupirocin twice daily for 5–10 days and topical body decolonization regimens with a skin antiseptic solution (e.g., chlorhexidine) for 5–14 days or dilute bleach baths. (For dilute bleach baths, 1 teaspoon per gallon (≈4 liters) of water [or ¼ cup per ¼ tub or 13 gallons (≈50 liters) of water] given for 15 min twice weekly for ≈3 months can be considered.) An oral agent in combination with rifampin, if the strain is susceptible, may be considered for decolonization if infections recur despite above measures (C-III). The concern for emergence of mupirocin resistance is mentioned; and a warning that “bleach baths” are recommended, patients need to be given clear instructions given the potential for skin irritation if not adequately diluted.

**BACTEREMIA AND ENDOCARDITIS**

MRSA bacteremia is associated with high morbidity and mortality. Recommendations for therapy include:

> For adults with uncomplicated bacteremia (defined as patients with positive blood culture results and the following: exclusion of endocarditis preferably by transesophageal echocardiography (TEE); no implanted prostheses; follow-up blood cultures performed on specimens obtained 2–4 days after the initial set that do not grow MRSA; defervescence within 72 h of initiating effective therapy; and no evidence of metastatic sites of infection), vancomycin (A-II) or daptomycin 6 mg/kg/dose IV once daily (A-I) for at least 2 weeks. For complicated bacteremia (defined as patients with positive blood culture results who do not meet criteria for uncomplicated bacteremia), 4–6 weeks of therapy is recommended, depending on the extent of infection. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (B-III).

> For adults with infective endocarditis, IV vancomycin (A-II) or daptomycin 6 mg/kg/dose IV once daily (A-I) for 6 weeks is recommended. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (B-III).

The guideline re-emphasizes the principle that MSSA should preferably be treated with a beta-lactam agent, which has been known to be more effective than vancomycin for infections due to susceptible isolates. In addition, with the exception of prosthetic valve endocarditis, neither rifampin nor gentamicin is recommended in combination with vancomycin. The use of rifampin combination therapy in a study of native valve *S. aureus* endocarditis did not improve outcomes but was associated with hepatic adverse effects, drug interactions, and the emergence of resistance (Riedel DJ, Weekes E, Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by *Staphylococcus aureus*. Antimicrob Agents Chemother 2008; 52:2463–7). For prosthetic valve endocarditis, the recommendation is IV vancomycin plus rifampin 500 mg PO/IV every 8 h for at least 6 weeks plus gentamicin 1 mg/kg/dose IV every 8 h for 2 weeks (B-III) in addition to valve replacement.
MRSA can cause a severe, necrotizing pneumonia with high mortality rate. Recommendations for therapy include:

- For HA-MRSA or CA-MRSA pneumonia, IV vancomycin (A-II) or linezolid 600 mg PO/IV twice daily (A-II) or clindamycin 600 mg PO/IV three times daily (B-III) if the strain is susceptible, is recommended for 7-21 days, depending on the extent of infection.

Linzolid would appear to have some theoretical advantages which include better pharmacokinetics into the lung and the possibility to reduce toxin production for CA-MRSA. Despite this, there remains controversy based on different results of pooled analyses and meta-analyses of clinical trials. Of note, the results of the Zephyr study were not available at the time of the completion of the guideline. This study of MRSA VAP which was reported at IDSA in Oct, 2010 (Kunkle M et al Abstract LB-49), found a clinical benefit of linezolid over vancomycin in the response rates of the per protocol population (57.5% vs. 46.5%, p=0.042) although there was no significant difference in mortality.

**VANCOMYCIN CONSIDERATIONS AND PERSISTENT BACTEREMIA**

From the laboratory standpoint, the most pertinent recommendations relate to vancomycin dosing and approach to the patient with clinical failure. In recent years, several centers have observed a “MIC creep” among MRSA isolates characterized as susceptible by *in vitro* criteria. However, this has not been a universal finding in all geographic areas. Nevertheless, several observational studies have shown that clinical failures appear to be more common among those with MIC values of 2 µg/mL than among those with MIC values < 2 µg/mL. In addition, the emergence of hVISA, VISA and VRSA has introduced a concern in using vancomycin. These strains are not common but have been associated with vancomycin treatment failures. The optimal assay most predictive of such isolates is unclear and testing for hVISA is not routinely recommended. For patients with an isolate with a vancomycin MIC of 2 µg/mL, particularly those patients with limited or no clinical response to vancomycin therapy, an alternate method, such as Etest®, should be performed to improve detection of VISA.

The guideline addresses the question of management of persistent MRSA bacteremia and vancomycin treatment failures in adult patients. Because the median time to clearance of MRSA bacteremia is 7–9 days, most experts agree that persistent bacteremia at or around day 7 of therapy should prompt an assessment to determine whether a change in therapy is indicated. In general, when constructing an alternate regimen in the setting of vancomycin treatment failure in adult patients, the guideline recommends a change in therapy rather than the addition of other agents (e.g., rifampin and gentamicin) to vancomycin.

Possible choices include:

1. Daptomycin (10 mg/kg dose), which has the most rapidly bactericidal activity although isolates with vancomycin MICs > 2 µg/mL may have daptomycin MICs in the non-susceptible range and *in vitro* exposure to vancomycin may select for higher daptomycin MICs.
2. Although there are no clinical data, some experts suggest the use of daptomycin in combination with another agent, such as gentamicin administered at a dosage of 1 mg/kg every 8 h, rifampin, or both drugs if the strain is susceptible to both.
3. Quinupristin-dalfopristin has been used successfully as salvage therapy in patients with vancomycin treatment failure, although response rates were lower for patients with endocarditis and bacteremia of unknown source.
4. TMP-SMX is bactericidal *in vitro*, but was inferior to vancomycin for the treatment of *S. aureus* infections, although all treatment failures occurred among those with MSSA infection, whereas all patients with MRSA infection were cured. Thymidine release from damaged host cells and bacteria may limit the efficacy of folate antagonists; so caution should be exercised when using TMP-SMX.
5. Linezolid has been used with some success in several series either alone or in combination with other agents (e.g., rifampin, fusidic acid, gentamicin, amikacin, and a carbapenem), but outcomes for patients with left-sided endocarditis have been poor. Of note, rifampin may decrease linezolid levels when given in combination via an unclear mechanism.
6. Telavancin has limited clinical experience.

### **REFERENCES**


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