Clinical and microbiological characteristics of community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections now occur in healthy adults in community settings. We searched the PubMed database to identify relevant articles on the clinical presentation, epidemiology, virulence, and treatment of community-acquired MRSA (CA-MRSA) infections, including pneumonia. This information was summarized in a narrative review.MRSA infections cause approximately 30 infections per 100,000 people per year in the USA, and twenty percent of these infections are secondary to CA-MRSA. These community-acquired infections often involve the skin and subcutaneous tissue but can also involve visceral tissues such as the lung and bone. The overall mortality in patients with invasive disease is approximately 10%; it approaches 50% in patients with pneumonia. The bacterial isolates from these infections have the staphylococcal chromosome cassette *mec* types 4 and 5. This genetic characteristic produces beta-lactam resistance and helps distinguish these isolates from hospital-acquired MRSA, which usually have *mec* types 1-3. Some CA-MRSA isolates release the Panton-Valentine leukocidin (PVL), which causes neutropenia and tissue necrosis; other toxins also contribute to the virulence of these infections. Empiric therapy should include vancomycin or linezolid. CA-MRSA infections can have fulminant courses and high mortality rates. Physicians should consider these infections as possible emergencies with a high risk for organ system failure and shock.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections first occurred in hospitalized patients or in patients who had previously been hospitalized. However, in the 1990's, MRSA infections began to occur in young, healthy adults in the community.[1] These latter infections have been called community-acquired MRSA (CA-MRSA) in contrast to hospital-acquired MRSA (HA-MRSA) and are the presumptive diagnosis when the criteria for HA-MRSA are not met.[2] Studies in these two groups of patients and with the associated bacterial isolates have demonstrated that there are important differences between CA- and HA- MRSA. We recently helped care for a fatal case of CA-MRSA pneumonia, and this stimulated us to review the clinical and microbiological characteristics of CA- and HA-MRSA infections.[3] We approached this review by answering important clinical questions about these infections to update clinicians who take care of patients with severe infections, especially pneumonia, in intensive care units (ICUs).

Materials and Methods

PubMed was searched to identify articles on MRSA infections to answer the questions discussed below. We used the following MeSH terms; methicillin-resistant *Staphylococcus aureus*, pneumonia, virulence factors, community-acquired infection, cross infection, *mec*A protein *S. aureus*, and epidemiology. MRSA was combined (AND) with the other MeSH terms and the text words Panton-Valentine leukocidin for searches. We used the following limits: published in the last 10 years, English only, and all adults: 19+ years. Reference lists from pertinent articles and from *related articles algorithm* provided by PubMed were also reviewed. This information was summarized to create a narrative review.

What is the epidemiology of methicillin-resistant *Staphylococcus aureus* infections in the US? What are the usual clinical presentations?

The prevalence of CA-MRSA infections and the typical clinical presentations clearly depend on the population studied. Kuehnert and coworkers determined the prevalence of staphylococcal colonization in a representative sample in the US population using the National Health and Nutrition Examination Survey.[4] This study involved 9622 subjects and demonstrated that 0.8% (95% CI: 0.4-1.4%) had nasal colonization with MRSA. This occurred more frequently in women and in participants older than 60. Fifty percent of the isolates had SCCmec IV genotype, 50% had the SCCmec II genotype, and 8% belonged to the USA300 clone (discussed below in the section on genetic studies). The prevalence of MRSA colonization increases in populations with health care associated risk factors, such as chronic dialysis, and some populations with close physical proximity, such as in jails and with some sports activities.

Caffrey and LaPlante reported information on the epidemiology of MRSA infections in the Veterans Affairs Healthcare System from 2002 through 2009.[5] This study demonstrated that the incidence of MRSA infections increased in all healthcare settings in the Veterans Affairs (VA) system, including hospitalized patients, patients in long-term care, and outpatients. The most common sites of infection involved the skin and soft tissue. Pneumonia occurred in 16% of the hospitalized patients and in 2% of the outpatients. Mortality rates were 6% for inpatients and 23% for patients in long-term care units. There was no information on mortality for outpatients since presumably patients this sick would be admitted to the hospital. The exact site of infection was unclear in approximately 50% of the outpatients in this study. Consequently, the frequency of some clinical syndromes associated with outpatient MRSA infections in this study is uncertain, and some types of infection are probably under reported. As expected, patients in this Veterans Affairs Healthcare System had significant co-morbidity. Twenty percent or more of the inpatient population had chronic renal disease, chronic respiratory disease, congestive heart failure, depression, diabetes, hypertension, and/or peripheral vascular disease. Important co-morbidity in the outpatient clinics included chronic respiratory disease (23%), depression (32%), diabetes (34%), and hypertension (62%).

The Active Bacterial Core Surveillance

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MRSA from the Centers for Disease Control and Prevention (CDCP) project provided national estimates of invasive MRSA infections and deaths. These Active Bacterial Core Surveillance reports classify MRSA infections into three categories.[6,7] Hospital-onset MRSA infections are defined as infections occurring more than two days after hospital admission. Health-care associated MRSA infections are defined as infections occurring ≤2 days after admission and having one or more of the following: i) a history of hospitalization, surgery, dialysis or residence in a long term care facility in the previous year, or ii) the presence of a central vascular catheter. Community-associated (acquired) MRSA infections meet none of the criteria for hospital-onset or health-care associated infections. In 2008, the Active Bacterial Core Surveillance MRSA study provided national estimates of invasive MRSA infections and deaths (29.5 infections per 100,000 and 5.0 deaths per100,000). Approximately 17% of the infections were community-acquired. CA-MRSA frequently infects a younger population (median age 30) and African-Americans (60.1 per 100,000 African Americans *vs.* 24.5 per 100,000 Caucasians).[6] While certain clinical presentations are more frequent in CA-MRSA infections than HA-MRSA infections, there are no unique associations, and Figure 1 illustrates the percent of cases associated with particular clinical presentations in 2008 collected by the CDCP Active Bacterial Core Surveillance program.[6] Most MRSA infections reported in this study presented with bacteremia (approximately 70% in CA-MRSA infections and >95% in HA-MRSA infections). Pneumonia occurs in 16% of patients with MRSA infections. The mortality rate in CA-MRSA cases was 9.8%; the mortality rates in hospital-onset and hospital-associated infections were 23.9% and 14.9 %, respectively. In summary, CA-MRSA infections often occur in younger, healthier persons and have a significant mortality rate, but this depends on the clinical setting. These CDCP reports provide information on selected populations with invasive disease. Therefore, the Veterans Affairs and the CDCP studies do not provide a comprehensive description of the epidemiology of the MRSA infections in the United States but do provide information relevant to hospitalized patients. The results in MRSA investigations will depend on case definition, population type, disease activity (endemic *vs.* epidemic), and completeness of microbiological investigations used to characterize the bacterial isolates.

Staphylococcal pneumonia usually develops after viral infections of the lower respiratory tract which allow staphylococcal adherence to epithelial surfaces and invasion.[3] Gillet and coworker reported studies on 16 patients with necrotizing pneumonia secondary to *Staphylococcus aureus* strains producing the Panton-Valentine leukocidin (PVL).[1] These patients were young with a median age of 15 and healthy. Seventy-five percent had an influenza-like syndrome prior to presentation. They presented with high temperatures, tachycardia, tachypnea, cyanosis, hypotension, and hemoptysis (38%). The median trough white blood cell was 1.8 kU/L, and the median trough platelet count was 70 kU/L. Most (86%) required mechanical ventilation, and the mortality rate was 75% even though none had an underlying disorder. Most of these bacterial isolates were methicillin-sensitive. Autopsies revealed massive ulceration of the tracheobronchial tree with adherent staphylococci and alveolar hemorrhage and necrosis with large clusters of staphylococci. Vardakas and colleagues recently analyzed case reports with PVL positive community-acquired pneumonia in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) and determined that these patients often have influenza-like symptoms, complicated hospital courses with acute respiratory failure and multiorgan system failure, and high mortality (50%).[8]

Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections frequently involve the skin and soft tissues and then disseminate to visceral organs such as lung and bone. Swaminathan and colleagues reported a case with staphylococcal skin abscesses complicated by septic arthritis, multiple metastatic bone and soft tissue infections, and cavitary pneumonia secondary to a community-acquired methicillin-sensitive *Staphylococcus aureus* infection which was PVL positive.[9] These authors suggested that their patient had the *PVL* syndrome characterized by necrotizing pneumonia, severe soft tissue and bone infection, and deep vein thrombosis (DVT). These patients are typically young and healthy and may or may not have a history of skin infection. The DVT presumably develops as a consequence of venous injury related to the adjacent cellulitis. Vardakas' literature review reported that DVT is relatively frequent in patients with both MRSA and methicillin-sensitive *Staphylococcus aureus* (MSSA) infections even without cellulitis and has a strong association with mortality.[8] Radiological studies have demonstrated that patients with MRSA pneumonia more frequently have peripheral infiltrates and bilateral pleural effusions than patients with MSSA pneumonia.[10] Patients with CA-MRSA pneumonia can have either segmental and non-segmental consolidation and/or nodules, and cavities can occur both in areas of consolidation and in nodules.[11] These patterns probably reflect different routes of lung infection and highlight the potential for necrosis in these infections.

How are genetic studies used to track the epidemiology of staphylococcal infections?

Multilocus sequence typing (MLST) is the preferred sequencing method to study the molecular evolution of *Staphylococcus aureus*.[12-16] By sequencing seven housekeeping gene loci (*arcC, aroE, glpF, gmk, pta, tpi and yqiL*), each strain of *Staphylococcus aureus* is

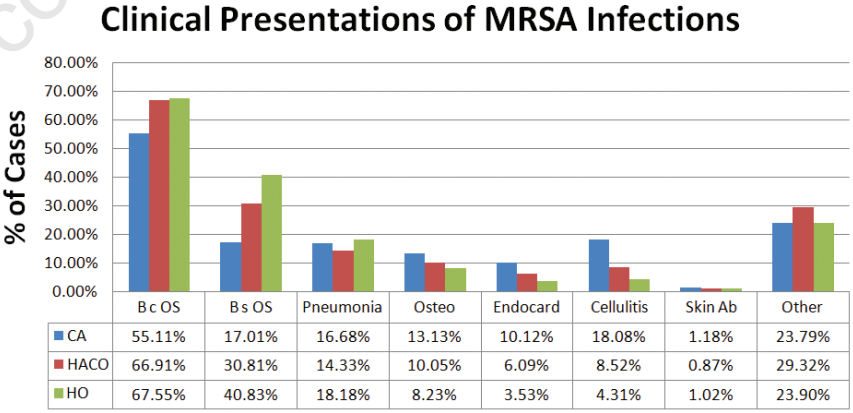

Figure 1. Values represent the percentage of a given clinical presentation of the total number of reported cases for a particular clinical classification. The percentages may exceed 100% because one infection may have several areas of clinical involvement. This information is based on the Centers for Disease Control and Prevention Active Bacterial Core Surveillance program (2008), and these results represent 929 cases with community-acquired Methicillin-resistant Staphylococcus aureus, 3203 cases with hospital-acquired Methicillin-resistant *Staphylococcus aureus*, and 1276 cases with hospital-onset-Methicillin-resistant *Staphylococcus aureus*. CA, community-acquired; HACO, health care-associated community onset; HO, hospital onset; BcOS, bacteremia with other syndromes; BsOS, bacteremia only; Osteo, osteomyelitis; Endocard, endocarditis; Skin Ab, skin abscesses, including skin abscesses, necrotizing fasciitis, gangrene, wounds.

assigned an allelic profile consisting of seven integers.[15] Each seven integer allelic profile defines a sequence type. Sequence types that match in ≥5 allelic positions are designated as a clonal complex, a group of *Staphylococcus aureus* that likely evolved from a single source.[13] There are multiple clonal complexes, each with many sequence types. Pulsed-field gel electrophoresis (PFGE) is also used to investigate HA-MRSA and hospital to hospital transmission.[15] This method uses digests of the bacterial DNA and gel electrophoresis to create patterns of DNA bands. PFGE differs from conventional electrophoresis because the voltage is sequentially applied to the gel in three different directions to increase the resolution of the bands. This allows researchers to examine large fragments of up to 40×10^6 base pairs, whereas conventional gel electrophoresis allows examination only of up to 50×10^3 base pairs of DNA.[16,17] The pattern of bands is used to identify (using reference standards) and compare isolates recovered in epidemiological investigations. In 2003, McDougal, *et al*. identified eight lineages designated as pulsed-field types USA100 through USA800. In order of decreasing prevalence, CA-MRSA infections are usually caused by USA types 300, 1100, 1000, and 500, and HA-MRSA infections are primarily caused by USA100 and 200.[18,19] Staphylococcal Protein A (spa) is another sequence-based method to determine genetic relatedness of Staphylococcal isolates using the variable region of an internal fragment of a single gene. Studies in Europe using *spa* typing suggest that there is more geographic clustering in MRSA isolates than MSSA isolates and that that MRSA isolates have less genetic diversity.[20] Faria and coworkers compared typing methods using both MRSA and MSSA strains and suggested that PFGE and *spa* typing provide good discrimination (typing) for local epidemiological studies and can suggest clonal relationships and lineages.[20] Finally, SCC*mec* typing (see section below on methicillin resistance) is also used to characterize MRSA isolates. Table 1 provides a summary of the genetic characteristics of four important US clones. MLST, PFGE, SCCmec, and *spa* typing clearly help characterize bacterial isolates causing infection and allow epidemiological tracking. These methods do not provide unequivocal identification of the origin staphylococcal isolates. In addition, the absence of the HA-MRSA criteria used by the CDCP does not consistently predict the presence of common CA-MRSA associations, such as clindamycin/ciprofloxacin susceptibility, the presence of SCC*mec* IV or V, the presence of PVL, and a lack of MRSA history.[21,22] This difficulty in making an accurate diagnosis of either CA- or HA-MRSA with current criteria indicates a need for different approaches to classifying these bacteria. This has become even more important since recent MRSA multi-locus sequence typing and pulsed-field gel electrophoresis studies have demonstrated that CA-MRSA can occur in hospital environments.[22,23]

Why are methicillin-resistant *Staphylococcus aureus* isolates resistant to methicillin?

SCC*mec* typing by PCR directly identifies methicillin sensitivity or resistance.[24,25] SCC stands for staphylococcal cassette chromosome, which is a genomic island, also called a mobile genetic element, passed between staphylococcal bacteria by an unknown mechanism(s). Traditionally, the SCC*mec* element has been thought to consist of a *mec* complex, cassette chromosomal recombinases (ccr), additional drug resistance genes, and junkyard regions (J). The *mec* complex carries the *mec*A gene, whose protein product is a penicillin-binding protein that has no or limited affinity for β-lactam antibiotics and thus confers β-lactam resistance.

There are seven different SCC*mec* types depending on different base sequences of the *mec* complex and the ccr genes. SCCmec types are clinically relevant since type I, IV, V, VI, and VII only carry resistance to β-lactam antibiotics. Type IV is typically found in CA-MRSA and represents a key difference from HA-MRSA (Tables 1 and 2).[18] CA-MRSA is susceptible to non-β-lactam antibiotics, with some exceptions, while HA-MRSA, typically associated with SCCmec types II and III, usually carry drug resistance genes to tetracyclines, flouroquinolones, macrolides, aminoglycosides, lincosamides, glycopeptides, and streptogramins.[26-28] Pulsed-field type USA300 (ST8

Table 1. Genetic analysis of Methicillin-resistant *Staphylococcus aureus* isolates.

Example	PFGE Clone	MLST	SPA	*mec*A gene	Comment
#1	USA100	ST 5	TJMBMDMGMK	II	Hospital-acquired
#2	USA200	ST 36	WGKAKADMQQQ	II	Hospital-acquired
#3	USA300	ST 8	YHGFMBQBLO	IV	Community-acquired
#4	USA400	ST 1	VJJJFF	IV	Community-acquired

PFGE, pulsed-field gel electrophoresis; MLST, multilocus sequence type; SPA, *staphylococcal* protein A motif (nomenclature for pattern of repeat base pair sequences in the C-terminal region of the protein A gene).

Table 2. Genetic differences between community-acquired Methicillin-resistant *Staphylococcus aureus* and hospital-acquired Methicillin-resistant *Staphylococcus aureus.*

Phenotype/Genotype	Function	Assay	HA-MRSA	CA-MRSA
Staphylococcal Chromosomal Cassette (SCCmec)	β lactam resistance, additional drug resistance, virulence role (PSMmec)	Multiple	II, III	IV, V
Panton-Valentine Leukocidin (PVL)	Cytolysis	Multiple	(-)	(+)
Phenol Soluble Modulin (PSM)	Cytolysis, hemolysis, inflammation	Multiple	(+)	(+)
Toxic Staphylococcal Shock Toxin (TSST-1),	Toxic shock syndrome	Some	(+)	(-)
Enterotoxins	Gastroenteritis	Some		
Accessory Gene Regulator (Agr)	Quorum-sensing, determines adhesion or exotoxin phenotype	Some	II, III	I, III (USA 1100 only)

HA-MRSA, hospital-acquired Methicillin-resistant *Staphylococcus aureus*; CA-MRSA, community-acquired Methicillin-resistant *Staphylococcus aureus*. This table presents an overview of approaches to characterizing MRSA isolates and is not meant to be comprehensive.

when MLST is used) is responsible for up to 97-99% of CA-MRSA infections and is typically associated with SCC*mec* type IV.[26] Diep and coworkers suggested that the only biological marker that completely differentiates CA-MRSA from HA-MRSA is the SCC*mec* type. According to his 2006 study, all CA-MRSA strains (USA300, 500, 1000, and 1100) carried SCC*mec* IV. In contrast, all HA-MRSA strains (USA100 and 200) carried SCC*mec* II.[17]

Do studies on virulence factors explain the pathogenesis of methicillin-resistant *Staphylococcus aureus* infections?

Despite its broader antibiotic sensitivity, CA-MRSA has pronounced virulence and can cause life-threatening infections, such as necrotizing fasciitis, necrotizing pneumonia, and severe staphylococcal sepsis.[26-30] Since these presentations occur less frequently in HA-MRSA infections, CA-MRSA must have either unique virulence factors, different combinations of virulence factors, or overexpression of common staphylococcal virulence factors when compared to HA-MRSA. Diep's analysis of 34 virulence factors in well characterized isolates of MRSA demonstrated that Panton-Valentine Leukocidin (PVL) was the only factor unique to USA300 and 1100 strains (the most common causes of CA-MRSA infections) and was not present in USA 500 and 1000 strains.[31] PVL positive clinical isolates have a strong association with severe CA-MRSA infections, and experimental studies support PVL's role in the pathogenesis of pneumonia.[8,28,29,31-35] Diep and co-workers have demonstrated that MRSA strain USA300 causes necrosis, edema, and hemorrhage in a rabbit model for pneumonia.[36] In addition, purified PVL toxin inoculated into the rabbit lung recruits and lyses neutrophils in the lung, resulting in inflammation and mortality. Labandeir-Rey et al. demonstrated that PVL positive *Staphylococcus aureus* strains caused pneumonia in a murine model and that purified toxin caused lung lesions and a high mortality rate.[37] The PVL toxin induces pores in neutrophils, increases permeability, and causes cell lysis. Hongo investigated the lytic activities of both phenol soluble modulin $\alpha 3$ (PSM$\alpha 3$) and PVL in human and murine models.[25] Both proteins caused neutrophil lysis, and the rate was significantly greater when both PSM$\alpha 3$ and PVL were present, suggesting a synergistic effect of these two exotoxins.[25] However, Bubeck Wardenburg and coworkers have reported that PVL does not contribute to the pathogenesis of staphylococcus infection in some strains of mice.[38,39] CA-MRSA strains also have other virulence factors, including α, δ, and γ hemolysins. Bubeck Wardenburg demonstrated that alpha hemolysin causes lung injury in a murine model for staphylococcal pneumonia.[38,39] Consequently, the virulence of CA-MRSA isolates potentially involves several toxins and cannot be consistently attributed to a single toxin, such as PVL.

CA-MRSA's increased virulence could reflect differential exotoxin expression. PVL secretion, along with other staphylococcal exotoxins, is regulated by *agr* (accessory gene regulator).[40] The accessory gene regulator is a quorum-sensing control that reacts to bacterial density by changing the transcription rates of two divergent operons controlled by promoters P2 and P3 and has a pivotal role in the expression of staphylococcal exotoxin genes. The accessory gene regulator is classified into four different types (namely, *agr* I, II, III, and IV).[41,42] In Diep's study, three *agr* types were included in his virulence factor panel. CA-MRSA strains almost uniformly have the *agr* I genotype; HA-MRSA strains have a mixture of *agr* II and III genotypes. The *agr* genes positively regulate the expression of all *S. aureus* hemolysins, PVL, PSM, and the majority of *S. aureus* proteolytic enzymes; this gene regulator likely has a crucial role in CA-MRSA-induced leukopenia and parenchymal necrosis.[40,43] Strains associated with *agr* I have been associated with invasive infections, particularly bacteremia, while strains with *agr* II and III regulators were more frequently associated with non-invasive infections.

CA-MRSA infections frequently cause skin infections and abscesses. *Staphylococcus aureus* secretes coagulase and von Willebrand factor-binding protein.[44] These proteins bind to and activate prothrombin which cleaves fibrinogen to fibrin which in turn promotes abscess formation. Staphylococci replicate in the center of abscesses and potentially enter the circulation following rupture of abscess capsules. Therefore, CA-MRSA virulence depends on the presence of certain toxins and proteins (*e.g.,* PVL, alpha hemolysin, coagulase), the production of these toxins and proteins (controlled by the number of gene copies and the *agr* regulation), and the presence or absence of antibody to the toxin(s).[43] The pathogenesis of MRSA infections also involves complex interactions between the bacterial proteins, such as coagulase, and the host defenses. Specific antibodies to some staphylococcal proteins confer protection.[44]

How do clinicians and hospitals identify methicillin-resistant Staphylococcus aureus?

The initial identification and classification of MRSA infections largely depends on the CDCP Active Bacterial Core Surveillance definitions. Laboratory identification of MRSA typically depends on bacterial cultures which require 20 h with the use of chromogenic media for reliable negative results.[45] However, isolation and sensitivity testing, along with confirmation, requires an additional 24 to 48 h.[46] In cases with possible PVL-positive hypervirulent CA-MRSA infections, this delay in diagnosis could prove fatal. Thus clinicians need real-time identification of MRSA and PVL. MRSA can be identified by the presence of SCC*mec*, and SCC*mec* typing can usually distinguish CA from HA-MRSA. However, the primary purpose of early identification of CA-MRSA infections is to initiate empiric antibiotic coverage and anticipate complications. Several researchers have developed methods for rapidly identifying a variety of staphylococcal virulence factors, including SCC*mec* and PVL.[47,48] Tables 1 and 2 list several of the distinguishing differences between CA and HA-MRSA. These methods have not been introduced into routine work in most clinical laboratories.

What are the treatment and prevention implications?

The overall mortality for invasive CA-MRSA infections in the CDCP data collection was 10%.The mortality rate for CA-MRSA necrotizing pneumonia is approximately 50%, and most patients require mechanical ventilation. The usual diagnostic testing required to identify MRSA depends on current culture methods with unavoidable delays. Therefore, clinicians need to consider the possibility that MRSA is responsible for community-acquired infections and choose antibiotics to cover this pathogen. The Infectious Disease Society of America guideline published in 2011 recommends empiric coverage for MRSA in patients with community-acquired pneumonia if they require ICU admission, have necrosis, or have empyema. This represents an A-III recommendation based on expert opinion.[49] Vancomycin is the first line treatment and should be used in doses to achieve trough levels of 15-20 µg/mL. However, after a positive culture for MRSA is identified, it is important to determine the vancomycin minimum inhibitory concentration for that particular isolate. Recent studies have demonstrated that *Staphylococcus aureus* isolates have reduced vancomycin susceptibility based on in vitro laboratory testing; this situation increases the potential for treatment failure, especially in patients with bacteremia. Reduced vancomycin sensitivity is usually defined as a minimal inhibitory concentration greater than 1 µg/mL. Mascitti and co-workers reported that approximately 34% of patients with MRSA infections have reduced vancomycin susceptibility.[50] This occurred in patients with both methicillin-sensitive *Staphylococcus aureus* infections and MRSA infections, and multivariate analysis of the data in this study indicated that reduced vancomycin susceptibility was

associated with prior inpatient vancomycin use, prior inpatient levofloxacin use, and methicillin resistance. If the minimum inhibitory concentration is near the breakpoint for susceptibility (2 μg/mL) or the clinical picture deteriorates, linezolid should be used. Linezolid is a bacteriostatic antibiotic with good penetration into lung tissue and is as least as effective as vancomycin in lung infections. Its side effects include thrombocytopenia, lactic acidosis, and neuropathy, especially with prolonged courses. A recent randomized trial compared linezolid with vancomycin in patients with MRSA nosocomial pneumonia.[51] This study indicated that the linezolid treated patients had a higher level of clinical success at the end of the study than vancomycin treated patients. The overall frequency of adverse events was similar, but nephrotoxicity occurred more frequently in patients treated with vancomycin (18%) than with linezolid (8.4%). Sixty day mortality rates were similar in the two groups. Daptomycin provides an alternative for treating patients with MRSA bloodstream infections and/or endocarditis. However, it is not useful in patients with pneumonia because of poor activity levels in the lung probably related to binding to surfactant in alveolar spaces. Patients with CA-MRSA skin and soft tissue infections can often be treated with trimethoprim-sulfa, doxycycline, and clindamycin, but these drugs are not adequate for the initial therapy of critically ill hospitalized patients. In addition, antimicrobials that suppress exotoxin production and secretion should be considered in cases with severe infection. Clindamycin decreases staphylococcal exotoxin production *in vivo* and *in vitro*, and some authors think that the initial therapy should include linezolid and clindamycin.[52] However, some staphylococcal isolates have inducible clindamycin resistance which can be detected in the laboratory using the *D test*. Inducible and constitutive clindamycin resistance occurs more frequently in MRSA isolates.[53] In very sick patients with multiorgan failure or shock, intravenous immunoglobulin might be considered since it neutralizes PVL *in vitro*.[33,54] It has been used in a small number of cases at doses of 2 gm per kilogram with a second dose at 48 h. Molecular diagnostic techniques can now provide relatively rapid identification of methicillin-resistant staphylococci on body surfaces and in clinical specimens (Table 2). Some healthcare systems have introduced screening for nasal colonization by MRSA in patients admitted to various hospital services. These screening protocols range from the selected screening in specialized populations, such as patients with a prior history of MRSA infection, to universal screening of all patients admitted to the hospital. This information can be used to determine which patients need contact isolation and can be used for clinical decision making in patients who present with clinical syndromes consistent with staphylococcal infection. In addition, some clinical services make an effort to eradicate nasal colonization with MRSA in patients who are at risk for staphylococcal infection following either surgery or various procedures, such as long term vascular catheterization. The approach to the management of patients with nasal colonization with MRSA must consider the following issues: i) MRSA colonization may resolve spontaneously and then recur; ii) Treatment of MRSA colonization with either oral or local antibiotics may not produce sustained eradication; iii) Given these uncertainties, selective eradication seems to provide the best strategy. For example, treating MRSA colonization in patients on chronic dialysis could potentially reduce the frequency of MRSA related infection.[55,56] In general, the management of colonized patients will depend on the prevalence of MRSA in the hospital and in select patient populations in that particular hospital, on the resources available for testing and treatment, and on the overall infectious control policies and priorities.

Conclusions

Many clinicians are not aware of the increased disease severity in hypervirulent MRSA infections. CA-MRSA infections can cause both severe fulminant disease including necrotizing pneumonia and chronic infections with multiple abscesses. Some but not all of these Staphylococcal strains secrete the PVL toxin. However, even if PVL- positive CA-MRSA were suspected, most clinical laboratories do not test for PVL. Better and faster identification methods would have both epidemiological and treatment implications. However, until this testing becomes available and is tested in clinical decision-making, clinicians need to understand the clinical importance of CA-MRSA and manage these patients as if shock and multiorgan system failure were inevitable. In some patients with possible MRSA infection the initial empiric therapy should include either vancomycin or linezolid.

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