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Research Article

Invasiveness and Risk Factors for Community-Acquired Methicillin-Resistant Staphylococcus Aureus (MRSA)

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Abstract

Background: MRSA is methicillin-resistant Staphylococcus aureus, risk factors for acquiring MRSA infection in the community are many from crowding and interaction with an asymptomatic carrier to a recent outpatient visit. CA-MRSA can cause a variety of problems ranging from are skin infections and sepsis to pneumonia to bloodstream infections.

Methods: Literature search in MEDLINE, CINAHL and Embase from 1990 to 2016). Texts and authoritative Web sites were also reviewed then identification of papers according to the inclusion and exclusion criteria and data extraction were performed by two independent researchers.

Results: Following data extraction and synthesis, we identified 45 articles for review. Information was organized into 6 clinically relevant categories for presentation which are microbiology, predisposing and risk factors for infection, Case reports and clinical presentation, diagnostic, screening of carriers and case reporting.

Conclusion: CA MRSA can be easily spread in the community with or without admission in a healthcare setting with high risk of horizontal transmission. CA-MRSA infection can cause serious morbidities which can rapidly progress with a serious clinical course and result in mortality if left untreated, thus awareness of the invasiveness, incidence and risk factors of CA-MRSA infection in the community is a compelling need.

Keywords: *Methicillin-resistant; Staphylococcus aureus; Public health; Pneumonia; CAP*

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is a common public health problem worldwide, with a long history of significant morbidity and mortality [1], since *Staphylococcus aureus* is armed with a variety of virulence factors that facilitate adherence of and invasion to host tissues in addition to structures that disable host defenses and toxins that induce septic syndromes [2].

Methicillin resistance is mediated by PBP-2a, a penicillin-binding protein encoded by the mecA gene that permits the organism to grow and divide in the presence of methicillin and other beta-lactam antibiotics. The mecA gene is located on a mobile genetic element called staphylococcal chromosome cassette (SCCmec). A single clone probably accounted for most MRSA isolates recovered during the 1960s; by 2004, six major MRSA clones emerged worldwide, labeled as SCCmec I to VI [3,4]. Dissemination of resistance was mediated by horizontal transfer of the mecA gene and related regulatory sequences [5].

S. aureus has acquired genes that promote resistance for several classes of antibiotics; the most important to date is the mecA gene that confers resistance to methicillin and almost all β-lactams [6].

MRSA strains associated with hospitals are referred to as hospital-acquired MRSA (HA-MRSA) and are the most common cause of hospital-acquired infections [7,8]. While Strains associated with the community are referred to as community-acquired MRSA (CA-MRSA) and are also present in people who serve as asymptomatic carriers [9]. Methicillin-resistant *S. aureus* is the leading cause of skin and soft tissue infection in patients reporting to emergency departments for treatment [10], with a rising rate in primary care clinics [11] and intensive care units. Invasive MRSA-related conditions most commonly reported include septic shock (56%), pneumonia (32%), endocarditis (19%), bacteremia (10%), and cellulitis (6%) [12].

Community-associated MRSA (CA-MRSA) has also increased; an incidence of 59% of CA-MRSA in skin and soft tissue infections was reported by emergency departments in 11 US cities13, making MRSA the most frequently isolated agent in this type of pathology. These figures, together with the risk of development of glycopeptide-resistant *S. aureus,* make the need for worldwide implementation of effective measures for the prevention of transmission of MRSA essential, both in hospitals and within the community.

From the clinical point of view, methicillin-resistant *S. aureus* (MRSA) has become the primary pathogen of skin and soft tissue infections, but invasive infections also occur [2-14]. Among them, nosocomial pneumonia (NP), healthcare-associated pneumonia (HCAP) and community-acquired pneumonia (CAP) are of major importance due to the morbidity and mortality attributed to them [15].

The strains associated with NP/HCAP and CAP have distinct characteristics. The former contains the staphylococcal cassette chromosome SCCmec types I-III, while the latter contains SCCmec types IV and V. In addition, community-acquired (CA)-MRSA strains are susceptible to more classes of antibiotics [16,17]. Finally, toxins like Panton–Valentine leukocidin (PVL) have been identified more frequently in CA-MRSA strains.

Materials and Methods

Literature search

We carried out a retrospective study of patients with from 1990 to 2016 (studies with relevant endpoints were found to be between 1993 and 2012).

Data Sources are MEDLINE (via PubMed) EMBASE and Cochrane Library.

Search terms are MRSA, methicillin-resistant Staphylococcus aureus, and Staphylococcus aureus.

Data extraction

Search results were screened by scanning abstracts for the following Inclusion Criteria:

- Content of the article related to the epidemiology or/and clinical management of MRSA
- Randomized controlled trials (RCTs), controlled clinical trials (RCTs), comparative studies, studies with irrelevant endpoints were excluded.

Two reviewers independently reviewed studies, abstracted data, and resolved disagreements by consensus. Studies were evaluated for quality. A review protocol was followed throughout. A total of 45 studies were reviewed.

Results

Searches identified 236 publications in addition to another 12 publications that were found through manual research. After removal of duplicates, abstracts and titles 219 publications were assessed as identified from title and abstract, and 54 papers were excluded. There were 10 papers full text could not be retrieved, also 30 papers excluded because they did not discuss the present study's relevant endpoint

(safety, complications and effectiveness of TT) and another 42 papers excluded for having the same cohort. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting the results.

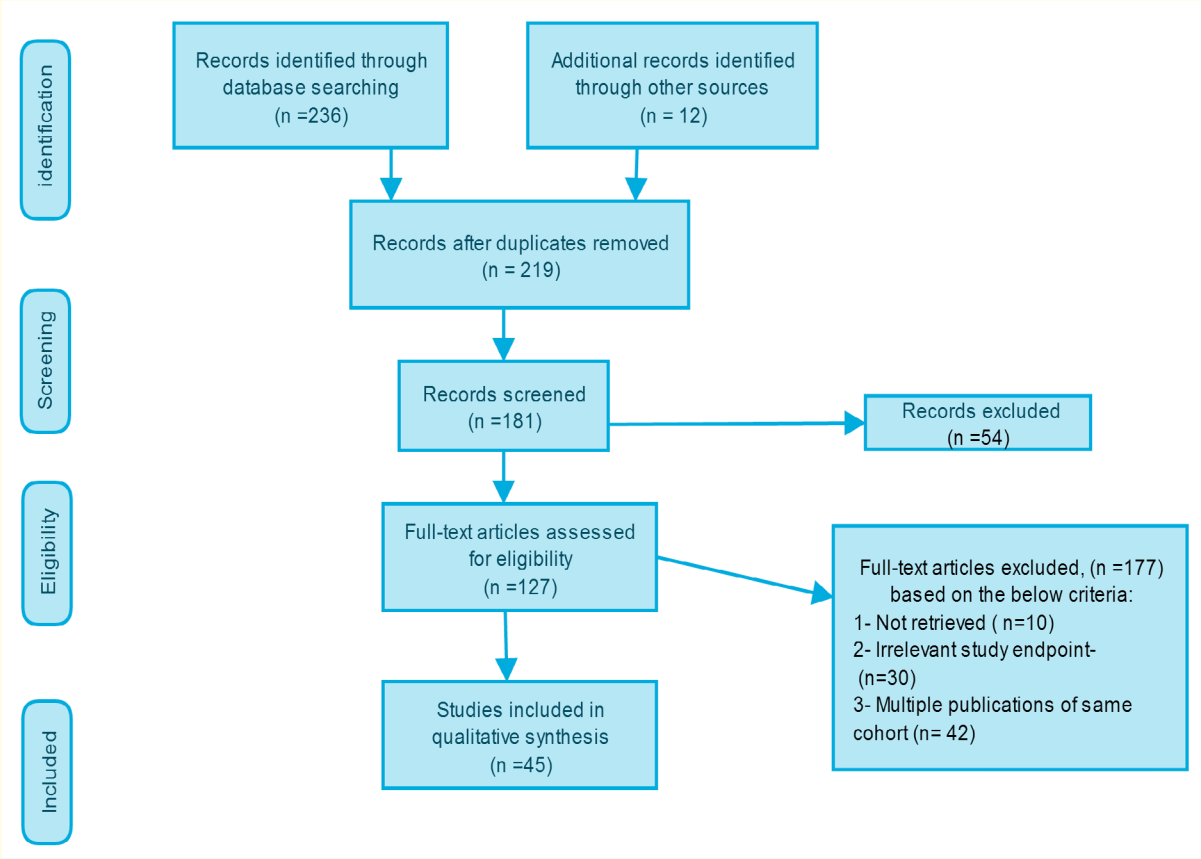

Figure 1: *PRISMA flow diagram showing the selection process and steps of the literature search.*

Finally, 45 publications were selected to be studied in the present review.

Microbiological classification of MRSA

Staphylococcus aureus is a gram-positive, nonmotile, pus-producing coccus [18]. Microscopically, *S. aureus* has the appearance of 0.5-1.5 μm balls that are clumped together, like grapes [19]. There are more than 200 strains of *S. aureus* [20]. *Staphylococcus aureus* possesses several virulence factors that, combined with its increasing antibiotic resistance, contribute to its success as an infective agent [19].

Predisposing and risk factors for CA-MRSA

In general terms, the primary risk factor for MRSA infection in the inpatient setting is a compromised immune system. Those most at risk for infection are infants, [20] the elderly, [21,22] the chronically ill, [23] burn survivors, [20] organ transplants recipients, cancer patients receiving chemotherapy agents, [24] steroid users, [24] diabetic patients, [7] intravenous drug users, and those with AIDS [7]. However, in the outpatient or community setting, risk factors for CA-MRSA infection include exposure to an individual with MRSA, usually skin-to-skin contact, and exposure to environments favorable to crowding [23] or a lack of cleanliness [21,25]. Community-acquired MRSA is more common in competitive athletes [9,21], military personnel [9,21,56], and prison inmates [9,21,27]. In the community, MRSA tends to affect younger, healthier people [21,22] such as college students [28]. Outbreaks have also been reported in children [9,29], the home-

less [9,21], men who have sex with men [47], some Native American groups [21], and injection drug users [30]. The CDC advocates the "5 Cs" (crowding, frequent skin-to-skin contact, compromised skin, contamination, lack of cleanliness) as important to MRSA transmission.

Case reports of CA-MRSA

A study conducted by Centers for Disease Control and Prevention (CDC) 31,Atlanta, USA in 2008- Table 1- has reported a higher rate for Bloodstream Infection (57%), Osteomyelitis (13%), Endocarditis (10%), Cellulitis (18%) caused by CA-MRSA compared to hospital-onset (HO) cases ; where MRSA culture was obtained on or after the fourth calendar day of hospitalization, where admission is hospital day 1 and healthcare-associated community-onset (HACO) cases where the culture was obtained in an outpatient setting or before the fourth calendar day of hospitalization and had one of more of the following: 1) a history of hospitalization, surgery, dialysis, or residence in a long term care facility in the previous year, or 2) the presence of a central vascular catheter within 2 days prior to MRSA culture.

Syndrome[a]	CA (n=948)	HACO (n=3,282)	HO (n=1,298)	CA	HACO	HO
Bloodstream Infection with other syndrome	223	1,187	597	24%	36%	46%
Bloodstream Infection with no other syndrome	536	1,670	479	57%	51%	37%
Pneumonia	155	468	234	16%	14%	18%
Lower Respiratory Infection[b]	50	105	94	5%	3%	7%
Osteomyelitis	120	335	109	13%	10%	8%
Endocarditis	92	200	46	10%	6%	4%
Cellulitis	166	284	59	18%	9%	5%
Wounds - Surgica[l]c	6	174	44	1%	5%	3%
Wounds - Decubitus/Pressure Ulcers	18	101	21	2%	3%	3%

Table 1*: Reported Clinical Syndrome by Epidemiologic Class.*

HO: hospital-onset, if the MRSA culture was obtained on or after the fourth calendar day of hospitalization; HACO: healthcare-associated community-onset, f the MRSA culture was obtained on or after the fourth calendar day of hospitalization if the culture was obtained in an outpatient setting or before the fourth calendar day of hospitalization and had one of more of the following: 1) a history of hospitalization, surgery, dialysis, or residence in a long term care facility in the previous year, or 2) the presence of a central vascular catheter within 2 days prior to MRSA culture; CA: Community acquired; if none of the previously mentioned criteria are met.

[a]Some case patients had more than one syndrome.

[b]Lower Respiratory Infection is defined as: a patient with pneumonia documented in their discharge summary, who has a positive MRSA non-sterile respiratory specimen with accompanying chest radiology results documenting any of the following: bronchopneumonia/pneumonia, air space density/opacity, new or changed infiltrates.

[c]Combines deep tissue/organ infection and infection of a surgical wound, post operatively.

[d]Category includes skin abscess, necrotizing fasciitis, gangrene, non-traumatic wounds.

S. aureus is responsible for 1-10% of Community-acquired pneumonia (CAP) cases reported in the literature [32].

We have identified seven case series discussing CAP published between 1993 and 2007 for a comparative study. The findings concurred with a systematic review conducted by Vardakas., *et al*. [33] on Incidence, characteristics and outcomes of patients with severe community acquired-MRSA pneumonia.

The characteristics of patients reported in these case series are shown in table 2 while outcome is presented in table 3. A total of 98 patients with MRSA CAP were included in these series. Of these, 52% of patients were male and 31% (for whom data was available) had risk

factors for CA-MRSA. Influenza like symptoms was present in 57% of patients; influenza infection was documented by culture or serology in 38%. Radiographic or autopsy findings of necrotizing pneumonia were reported for 61% of patients. All patients who did not die in the emergency department or during transfer to another hospital were admitted to the hospital, of which 85% required ICU treatment. The duration of hospitalization varied between studies but, in general, the median length of stay was prolonged (>13 days). Finally, overall mortality was 39%; data regarding mortality attributable to MRSA CAP was not available.

The characteristics of patients with MRSA CAP were not reported separately. However, it was reported that appropriate empiric therapy was instituted in 43% of MRSA patients and 100% of MSSA patients. An interesting finding of this study was that empiric antibiotic therapy was initiated sooner in patients who died than those who survived (median 2 versus 5 days). In addition, median length of stay was shorter for influenza positive than influenza negative patients (16 versus 8.5 days). Leukopenia was associated with death in multivariate analysis. Kallen., *et al.* emphasized that the limitations of their study were its retrospective design, the possibility of reporting only more severe cases, the isolation of *S. aureus* mainly from sputum specimens that increased the probability to include patients simply colonized with *S. aureus* and the difficulty in collecting data regarding a preceding or concomitant influenza infection.

Study	Year of Study	Gender Male/Female	Age (years)	MRSA presentation	Comorbidities	MRSA risk factors	Resistance to antibiotics#
Leroy 111	1993	NA	NA	12/14 (86)	NA	NA	NA
Hageman 108	2004	8/9 (47)	21 (0.25–62)	15/17 (88)	5/17 (29)	4/17 (24)	ERM 100 CLN 91LEV 55
Gonzalez 110	2005	12/2 (86)	13 (10–15)	12/14 (86)	2/14 (14)	1/14 (7)	ERM 100
Janvier 109	2006	NA	NA	5/5 (100)	NA	NA	NA
Castaldo 106	2007	5/2 (71)	14.2 (0.8–16)	7/7 (100)	0/7 (0)	NA	NA
Kallen 105	2007	21/30 (41)	16 (<1–81)	37/51 (73)	27/48 (56)	13/31 (42)	ERM 93LEV 50
Centers for Disease Control 107	2007	5/5 (50)	17.5 (0.3–48)	10/10 (100)	1/10 (10)	4/10 (21)	ERM 100 CLN 20LEV 20
Total		51/48 (52)	NA	98/118 (83)	35/96 (36)	22/72 (31)	NA

Table 2*: Characteristics of cases presented by the selected 8 studies for patients with (MRSA) community-acquired pneumonia (CAP).*

Study	Influenza like symptoms	Proven influenza infection	Necrotizing pneumonia	PVL production	Hospitalization	ICU treatment	Appropriate empirical therapy	Length of stay days	Death	Symptom onset to death days
Leroy 111	NA	NA	NA	NA	109/118 (92)¶	NA	2/10 (20)	NA	3/14 (21)	NA
Hageman 108	17/17 (100)	12/17 (71)	4/16 (25)	11/13 (85)	5/5 (100)	13/16 (81)	12/15 (80)	13 (1–108)	5/17 (29) +	7 (3–73)
Gonzalez 110	1/14 (7)	1/14 (7)	NA	14/14 (100)	14/14 (100)	14/14 (100)	NA	24.5 (1–120)	3/14 (21)	5 (2–7)
Janvier 109	NA	0/5 (0)	5/5 (100)	5/5 (100)	14/14 (100)	NA	NA	24 (5–42)	1/5 (20)	NA
Castaldo 106	NA	NA	7/7 (100)	NA	10/10 (100)	7/7 (100)	NA	30 (5–53)	3/7 (43)	30 (5–51)

Kallen 105	22/47 (47)	11/33 (33)	NA	16/17 (94)	7/7 (100)	34/43 (74)	26/51 (51)	16 (2–19)	24/47 (51)	4 (1–33)
Centers for Disease Control 107	10/10 100)	6/10 (60)	7/10 (70)	10/10 (100)	16/17 (94)¶	NA	NA	NA	6/10 (60)	3.5 (2–25)
total	50/88 (57)	30/79 (38)	23/38 (61)	56/59 (95)		68/80 (85)	21/76 (53)	NA	45/114 (39)	NA

Table3*: Clinical manifestation of cases presented by the selected 8 studies for patients with (MRSA) community-acquired pneumonia (CAP).*

In ambulatory health care and community settings, the majority of MRSA infections are cutaneous, involving cellulitis, an abscess, or both [21]. Simple inspection and basic health history questions will provide much information in the identification of MRSA. Pain and pus production at the site of infection are characteristic of *S. aureus* infections [34], and the infection is often accompanied by inflammation and swelling [21,30,35,36]. Cutaneous MRSA lesions will frequently occur at the site of an abrasion or cut, even if the injury is mild [30,36]. For example, athletes with artificial turf abrasions or who have used cosmetic shaving have developed MRSA skin infections [37]. Manual therapists should be vigilant for cutaneous staphylococcal lesions, such as cellulitis [21], abscesses, folliculitis [35,38], furuncles, carbuncles, erysipelas, and impetigo [30]. Methicillin-resistant *S aureus* should be considered as a potential diagnosis for any pus-producing skin lesion. For cutaneous CA-MRSA, differential diagnoses may include spontaneous abscesses [21] and lesions that appear to be spider bites.

CA-MRSA diagnosis

On isolating any MRSA strains with clinical and epidemiological suspicion of CA-MRSA, further laboratory characterization needs to be undertaken to support the diagnosis. SCCmec typing is performed by determining the combination of two attributes: the class of the mec gene complex, and with the type of the ccr (chromosomal cassette recombinase) gene complex. The former comprises classes A to C, and the latter comprises types 1-3. The technique employed is polymerase chain reaction (PCR), either using individual reactions or in a multiplex format [41]. In addition, the presence of the PVL gene is also detected by PCR [42]. The turnaround time of these molecular characterization tests is one day. Currently in Hong Kong, MRSA strains harboring SCCmec type IV or V, together with the presence of the PVL gene, are designated CA-MRSA. Although CA-MRSA strains are generally considered to be susceptible to most non- lactam antibiotics, multi-resistant phenotypes are not uncommonly encountered, such that the presumptive designation of non-multi-resistant MRSA strains as CA-MRSA is not reliable.

Screening for carriers

One important aspect in the control of CA-MRSA is the screening of close contacts of patients for carriage of the strain, for example, nasal and axilla swabs. In the laboratory, these are inoculated onto selective medium containing antimicrobials to suppress the growth of competing organisms. Any suspected MRSA isolates will be subjected to identification, susceptibility testing and molecular characterization tests [43].

Reporting of cases

Although national reporting is not currently required, reporting of individual MRSA cases is mandatory in some states. For example, since 2008, the state of California has required severe infections or any clusters or outbreaks of MRSA to be reported [44]. Because policies pertaining to the reporting of MRSA infections are ever-developing, providers should check with their state health department to

determine if MRSA is considered reportable where they practice [25]. If a practitioner recognizes a concentration of MRSA cases, such as in a sports team or at a summer camp, obligatory reporting to public health authorities is required [24]. Hospitals are required to report MRSA infection rates within their hospital-acquired infection rates [45].

Discussion

Staphylococcus aureus is a common bacterium in humans and a potent pathogen possessing numerous virulence factors that enhance its opportunity to thrive [19].

Some strains of *S. aureus* have developed resistance to antibiotic medications, including methicillin and drugs in its class, giving such specific strains of *S. aureus* the deserved name of MRSA. This drug resistance has developed rapidly and continues to evolve with each new medication developed to combat this infectious agent.

Manual therapists who work directly with patients and athletes in the health care environment should be informed of this potentially harmful infection and take action to recognize and prevent it [39].

A large proportion of MRSA-positive persons may have acquired their strains outside the hospital setting, and their MRSA strains were non-multiresistant, showed an HVR type A, and differed genotypically from epidemic strains found in hospitalized patients. None of the epidemic multiresistant hospital strains were prevalent in non-hospitalized persons. MRSA may also emerge as a community-acquired pathogen as a consequence of horizontal acquisition of the mecA gene to a previously susceptible *S. aureus* strain type 40.

Conclusion

CA MRSA can be easily spread in the community with or without admission in a healthcare setting with high risk of horizontal transmission. CA-MRSA infection can cause serious morbidities which can rapidly progress with a serious clinical course and result in mortality if left untreated, thus awareness of the invasiveness, incidence and risk factors of CA-MRSA infection in the community is a compelling need.

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