Eur J Clin Microbiol Infect Dis (2013) 32:711–721
DOI 10.1007/s10096-012-1807-3

REVIEW

Incidence, characteristics, and outcomes of patients with bone and joint infections due to community-associated methicillin-resistant *Staphylococcus aureus*: a systematic review

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Received: 17 September 2012 / Accepted: 17 December 2012 / Published online: 20 January 2013

Abstract To summarize the published evidence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) bone and joint infections. PubMed and Scopus electronic databases were searched. The annual incidence of invasive CA-MRSA infections ranged from 1.6 to 29.7 cases per 100,000, depending on the location of the population studied; bone and joint infections accounted for 2.8 to 43 % of invasive CA-MRSA infections. Surveillance studies showed that patients <2 years of age are mainly affected. Incidence rates were higher in blacks. Sixty-seven case reports and case series were identified; the majority of the patients included were children. Vancomycin and clindamycin were used effectively, in addition to surgical interventions. Seven patients out of 413 died (1.7 %) in total. Chronic osteomyelitis developed in 19 patients (data for 164 patients were available). The published evidence for CA-MRSA bone and joint infections refers mainly to children; their incidence depends on the location and race of the population. Vancomycin and clindamycin have been used effectively for their treatment.

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Introduction

Worldwide, methicillin-resistant *Staphylococcus aureus* (MRSA) strains are among the most commonly isolated bacteria in patients requiring hospitalization or with significant healthcare exposure (HA-MRSA) [1–3]. The presence of the mecA gene, which induces resistance to almost all β-lactams is probably one of their most important characteristics [4]. At the turn of the 20th century, the first reports of community-associated MRSA (CA-MRSA) infections among healthy individuals (with no identifiable risk factors for HA-MRSA infections) and among injection drug users, incarcerated people, and athletes were published [5, 6].

Strains of MRSA are more frequently associated with skin and soft tissue infections, but more invasive infections, including bone and joint infections, also occur [4, 7]. In fact, MRSA has been identified as one of the most common causes of bone and joint infections [8, 9]. During the last decade CA-MRSA strains have been reported to be responsible for osteomyelitis or septic arthritis [10]. We sought to review systematically the available evidence in order to identify the incidence, characteristics, and outcomes of patients with CA-MRSA in bone and joint infections.

Materials and methods

Data sources

The studies included in this review were retrieved from searches performed in PubMed and Scopus (up to May 2012), using the search terms "bone and joint infections," "osteomyelitis," "septic arthritis," "spondylodiscitis," "spondylitis," "bursitis," "discitis" in combination with the terms "community-associated methicillin-resistant *Staphylococcus*

aureus" or "community-associated MRSA." References of the retrieved articles and relevant reviews were also hand-searched.

Study selection criteria

Studies reporting data on the incidence, characteristics, and outcomes of patients with CA-MRSA bone and joint infections were included in this review. Therefore, studies of any design that enrolled patients of any age could be included. Prosthetic joint infections were also eligible. Abstracts of scientific conferences and studies published in languages other than English, Italian, German, Greek, French, and Spanish were excluded. Studies not fulfilling the definition of CA-MRSA infection (as described below) were excluded, even if the titles indicated that they were reporting data on patients with CA-MRSA bone and joint infection.

Definitions

A case of CA-MRSA bone or joint infection was defined as disease compatible with osteomyelitis or septic arthritis, in which MRSA was cultured from blood, synovial fluid, or bone biopsy. A culture from wound or abscess was eligible in cases of clinically and/or radiographically diagnosed bone or joint infections complicated with abscess formation or fistula. The culture should have been taken in an outpatient setting or within 48 h after hospital admission, and with none of the following healthcare risk factors: use of broad spectrum antibiotics during the previous 6 months, recent hospitalization, residence in a long-term care facility, dialysis, surgery 1 year before the onset of illness or permanent indwelling catheter or percutaneous medical device [11]. Moreover, the definition was broadened to include cases in which the molecular typing methods (pulsed-field gel electrophoresis [PFGE], multi locus sequence typing [MLST] or other techniques) provided evidence of a community-associated strain. This was allowed in order to study the potential penetration of MRSA strains with "community-associated" characteristics into the hospital environment.

Results

Epidemiology incidence of CA-MRSA bone/joint infections

A population-based surveillance program in Atlanta (GA, USA) and Baltimore (MD, USA) and a hospital laboratory sentinel surveillance of 12 hospitals in Minnesota (USA) performed in 2001 and 2002 showed that the annual incidence of invasive CA-MRSA infections was 25.7 cases per 100,000 in Atlanta and 18.0 per 100,000 in Baltimore. Bone and joint infections were responsible for 2.8 % of these cases in Atlanta, 5 % in Baltimore and 6 % in Minnesota. In both Atlanta and Baltimore CA-MRSA were more common in patients aged <2 years; in Atlanta CA-MRSA infections were more common among blacks than whites in all age groups [12]. In the Active Bacterial Core surveillance system during 2004–2005 the annual incidence of invasive CA-MRSA infections ranged between 1.6 and 29.7 per 100,000 among different regions. In this surveillance, the higher incidence was seen in patients aged >65 years (8.9 per 100,000) and the lower in patients aged 2–17 years (0.6-0.8 per 100,000) [13]. Osteomyelitis accounted for 8.1 % of all cases. Finally, data from a prospective surveillance in Sweden showed that during the period 2003–2005 the annual incidence of CA-MRSA-invasive infections was 16.6 per 100,000; bone and joint infections accounted for 43 % of the cases [14].

Selected studies

The searches performed in PubMed and Scopus generated a total of 130 and 233 search results respectively. The process of study selection is shown in details in Fig. 1. A total of 67 studies were included in the review [5, 15–80].

Case reports of CA-MRSA bone/joint infections

Table 1 summarizes the data available from patients described in case reports of CA-MRSA bone and joint infections; data for 45 patients from 35 reports were available [15, 17, 19, 24, 25, 27, 31, 34, 36, 38, 39, 41, 42, 44–48, 51, 52, 54–57, 61, 62, 65–68, 71, 73, 80]. The majority of the patients were young (25 out of 45 [56 %] were children ≤14 years, 30 out of 45 [67 %] were younger than 30 years old and almost all [44 out of 45, 98 %] were younger than 65 years). Most of them were male (31 out of 45, 69 %) with no known risk factors for CA-MRSA infections except for a history of skin and soft tissue infections (12 out of 42, 29 %). The median duration of symptoms prior to the diagnosis or hospitalization was 6 days. Fever, local tenderness, and articular disability were the main symptoms. Osteomyelitis was the main diagnosis (either alone [32 out of 45, 71 %] or in combination with septic arthritis [4 out of 45, 9 %]). Long bones were mainly affected followed by vertebrae. Diagnosis was confirmed by X-rays, computed tomography (CT), magnetic resonance imaging (MRI), or scintigraphy. Further microbiological studies for the identification of toxins (Panton–Valentine leukocidin [PVL] positive in 14 out of 17) and typing (according to SCCmec type and MLST) was performed in 38 % of the cases. SCCmec IV was the predominant or sole type in all studies.

The majority of patients had bacteremia (27 out of 45, 60 %) with or without local complications, including abscesses, pyomyositis, and deep venous thrombosis. Sixteen patients had systemic complications, either on admission or

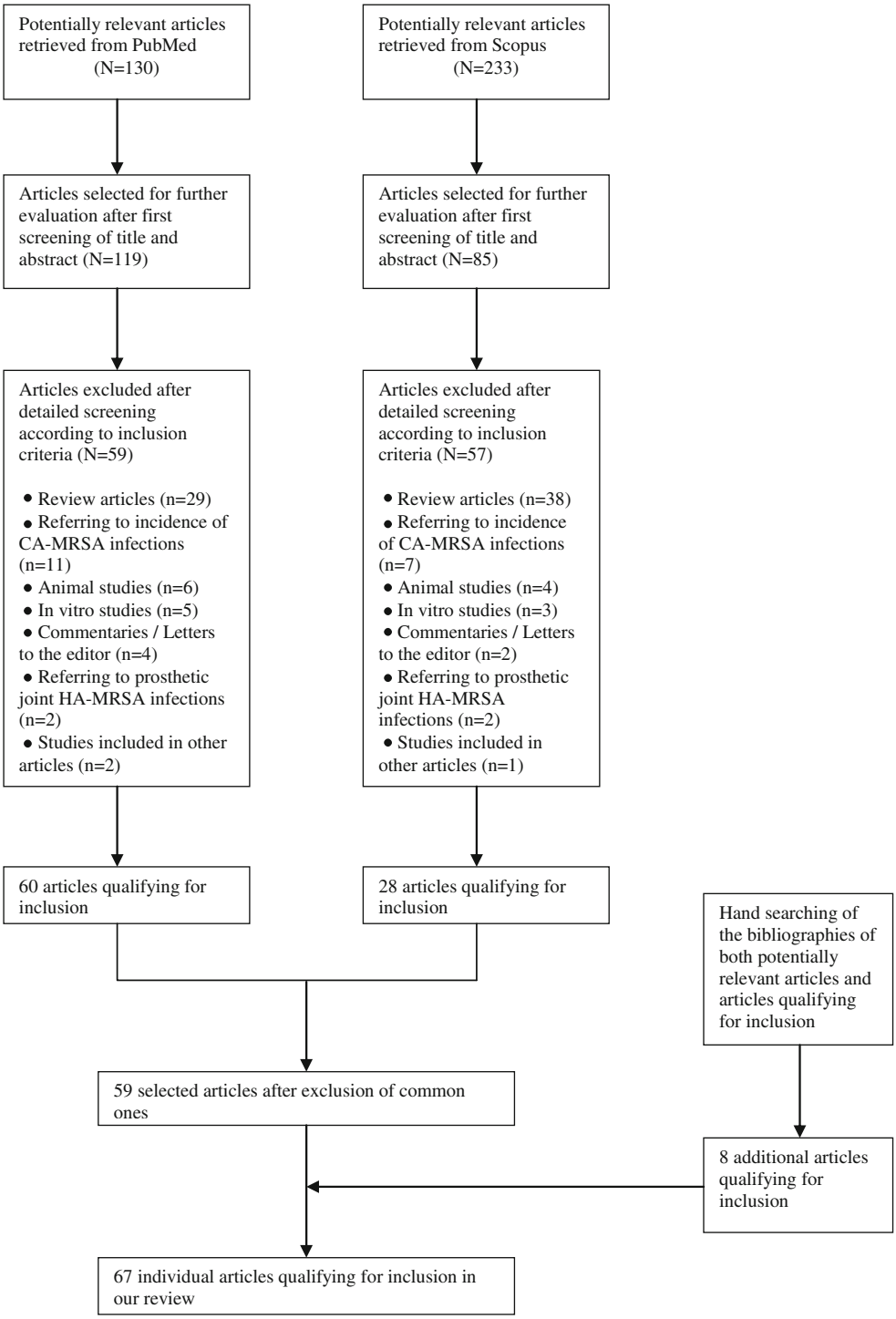

Fig. 1 Flow diagram of the detailed process of selection of articles for inclusion in the review

during treatment; 13 patients had pulmonary complications (mainly septic emboli and pleural effusion), 4 patients had central nervous system and 3 cardiac involvement.

The empirical treatment (before the culture results were available) was provided for 29 cases; in 16 of them (55 %) the empirical regimen did not include an antibiotic effective against MRSA. Following treatment that employed surgical interventions in 24 patients (59 %) and antibiotics in all patients (mainly vancomycin [36 out of 42, 88 %] and in some cases clindamycin, fusidic acid, linezolid, fosfomycin, trimethoprim/sulfamethoxazole or teicoplanin) for a median duration of 8 weeks (range 1–30), the majority of patients were cured (39 out of 44, 87.5 %), while 3 patients died (8 %). Two patients died during the first week of the hospital stay; 1 had chronic kidney disease and diabetes and 1 developed respiratory insufficiency due to septic emboli. The last patient died on week 5: a 7-year-old girl who developed respiratory insufficiency. Four recurrences were

Table 1 Main characteristics, interventions and outcomes of patients with community-acquired methicillin-resistant *Staphylococcus aureus* bone and joint infections

Parameter	
Demographics	
Age in years, median (range)	14 (0.3–75)
Male sex	31/45 (68.9)
Medical history[a]	
Diabetes	2/42 (4.7)
Orthopedic disease	4/41 (9.8)
Cardiovascular disease	4/43 (9.3)
Intravenous drug use	3/43 (7.0)
History of SSTIs	12/42 (28.6)
Clinical features on admission	
Duration of symptoms prior to hospitalization (median, days)	6 (0.5–90)
Fever (>37.5 °C)	33/40 (82.5)
Rash	4/37 (10.8)
Local redness	17/35 (48.6)
Local tenderness	34/38 (89.5)
Articular disability	24/42 (57.1)
Location of bone infection	
Long bones	28/36 (77.8)
Vertebrae	5/36 (13.9)
Other bones	4/36 (11.1)
Type of infection	
Osteomyelitis	32/45 (71.1)
Septic arthritis	9/45 (20)
Combined osteomyelitis and septic arthritis	4/45 (8.9)
Bacteremia	27/45 (60)
Local abscesses	21/44 (47.7)
Pyomyositis	14/44 (31.8)
DVT—after hospitalization	12/44 (27.3)
Systemic complications	15/39 (38.5)
Local complications	10/39 (25.6)
Cultures	
Bone	12/34 (35.3)
Synovial fluid	9/12 (75)
Other	11/39 (28.2)
Presence of PVL	14/17 (82.4)
Radiological diagnosis	
X-rays	15/26 (57.7)
CT	9/15 (60)
MRI	24/27 (88.9)
Scintigraphy	10/11 (90.9)
Treatment	
Duration (weeks, median)	8 (1–30)
Change of empirical treatment	17/30 (56.7)
Surgical treatment	24/41 (58.5)
Duration of hospital stay (weeks, median)	5 (1–13)
Outcomes	
Cure	35/40 (87.5)
Recurrence	4/40 (10)
Deaths	3/43 (7)

CT computed tomography, *DVT* deep venous thrombosis, *MRI* magnetic resonance imaging, *PVL* Panton–Valentine leukocidin, *SSTIs* skin and soft tissue infections

[a]Other co-morbidities were also reported, but their frequency was low

Table 2 Characteristics and outcomes of patients with CA-MRSA bone and joint infections in published case series

Reference	Patient age (years)[a]	No of patients	Location of the infection	Bacteremia	DVT	Presence of PVL	MRSA clone	used antibiotics after cultures	Survival
[23]	≤ 14.8 (mean= 7.6)	2	NR	NR	NR	NR	NR	IV vancomycin or teicoplanin	2/2 (100 %)
[69]	7.1	24	Non-axial osteomyelitis: 14, non-sacroiliac pyogenic arthritis: 8, axial infection: 2	NR	NR	NR	NR	Clindamycin or vancomycin	NR
[16]	8.9 (2.7–11.7)	47	Osteomyelitis: 23, septic arthritis: 7, both: 17	NR	2 (4.3 %)	Not tested	NR	IV clindamycin, vancomycin or cefazolin	47/47(100 %)
[34]	12.9 (mean)	12	Knee joint or multiple sites (bones and joints)	12 (100 %)	4 (33.3 %)	12 (100 %)	SCCmec type IVa	NR	10/12(83.3 %)
[49]	7.9±4.8	31	Osteomyelitis femur: 9, osteomyelitis tibia: 9, osteomyelitis other: 6, septic arthritis: 3, pyomyositis: 2	14 (45.2 %)	4 (12.9 %)	27 (87 %)	SCCmec type IV	Clindamycin, vancomycin or TMP-SMX	31/31 (100 %)
[30]	8.0±5.7	2	Osteomyelitis or septic arthritis	NR	NR	NR	NR	NR	2/2 (100 %)
[33]	8.1 (0.07–18)	41	Osteomyelitis: 38, septic arthritis: 3	NR	NR	41 (100 %)	NR	NR	40/41 (97.6 %)
[50]	5.0±4.7	19	Osteomyelitis: 14, septic arthritis: 5	13 (68.4 %)	NR	Not tested	NR	IV clindamycin or vancomycin	19/19 (100 %)
[53]	35.7±17.0	3	Osteomyelitis	NR	NR	NR	USA300	NR	3/3 (100 %)
[35]	10.6	7	Osteomyelitis of lower limb or pelvis	7 (100 %)	7 (100 %)	7 (100 %)	SCCmec type IV (USA300)	IV vancomycin	7/7 (100 %)
[74][a]	58.0±4.7	2	Osteomyelitis of the foot	NR	NR	NR	NR	NR	2/2 (100 %)
[22]	5.7	18	Hip joint: 10 (55.6 %), femur: 5 (27.8 %), tibia: 3 (16.7 %), and fibula: 1 (5.6 %).	17 (94.4 %)	0/18 (0)	NR	SCCmec type IV or V	NR	18/18 (100 %)
[72]	9.3	27	Osteomyelitis: 13, pyomyositis: 11, septic arthritis: 10, soft tissue or subperiosteal abscess: 6 and multifocal involvement: 13	15 (56 %)	7 (25.9 %)	NR	NR	IV vancomycin or clindamycin or linezolid with vancomycin	27/27 (100 %)
[18]	119.0± 53.8 months	56	Osteomyelitis of femur: 15, tibia/fibula: 20, other: 15, multiple sites: 9	39 (69.6 %)	NR	56 (100 %)	mostly USA300	NR	NR
[29]	9.63±5.42	2	Osteomyelitis or septic arthritis or both	NR	NR	2 (100 %)	European ST80	NR	2/2 (100 %)
[21]	9 months – 14.4 years	3	Septic arthritis knee: 2, septic arthritis hip: 1	3 (100 %)	NR	NR	NR	NR	3/3 (100 %)
[32]	3 weeks to 15 years	5	Osteomyelitis: 4, septic arthritis: 1	NR	NR	NR	NR	NR	NR

Table 2 (continued)

Reference	Patient age (years)[a]	No of patients	Location of the infection	Bacteremia	DVT	Presence of PVL	MRSA clone	used antibiotics after cultures	Survival
[77]	7 and 12 year respectively	2	Right tibia osteomyelitis: 1, left humerus osteomyelitis	NR	NR	NR	NR	NR	2/2 (100 %)
[78]	24 days, 1 month, 2 years, 12 years	4	Septic arthritis knee: 2, septic arthritis hip: 1, osteomyelitis tibia: 1	NR	NR	NR	NR	NR	4/4 (100 %)
[79]	3 (3 months to 12 years)	2	Septic arthritis (mainly hip and knee)	NR	NR	NR	NR	NR	NR
[59]	1 month to 50 years	3	Osteomyelitis of the femur or septic arthritis of the hip	3 (100 %)	2 (66.7 %)	3 (100 %)	SCCmec type IV	NR	3/3 (100 %)
[60]	9, 16, and 4	3	Septic arthritis of the right knee: 1, osteomyelitis of 3rd metatarsal: 1, osteomyelitis L tibia: 1	3 (100 %)	NR	3 (100 %)	SCCmec type IV	IV vancomycin plus PO clindamycin or rifampicin and fusidic acid	3/3 (100 %)
[64]	8.6 (4–12)	5	Osteomyelitis femur: 2, osteomyelitis tibia: 2, osteomyelitis scapula: 1	NR	NR	5 (100 %)	SCCmec type IV	IV clindamycin with or without vancomycin	5/5 (100 %)
[43][b]	58 (28–94)	5	Prosthetic joint infection	NR	NR	2 isolates	SCCmec type IV (USA300)[c]	NR	5/5 (100 %)
[28]	56.7±13.7	3	Lumbosacral, thoracic, or cervical tract spondylodiscitis	NR	NR	NR	NR	NR	NR
[70]	≥3 years	6	Osteomyelitis or septic arthritis	NR	NR	NR	NR	NR	NR
[75][b]	50±16	9	Osteomyelitis or septic arthritis or both or prosthetic joint infection	NR	NR	NR	NR	NR	9/9 (100 %)
[58]	36 months (median)	44	Osteomyelitis: 23, septic arthritis: 21	NR	NR	NR	NR	NR	NR
[37]	9.27(mean)	11	Osteomyelitis: 2 (hip), 7 (lower extremity), 1 (spine), 1 (upper extremity)	NR	NR	NR	NR	NR	10/11(90.9)
[26]	10.5 (median; range 1–15 years)	16	Osteomyelitis: 16	NR	7/16 (43.7 %)	NR	NR	IV vancomycin ± rifampicin followed by oral clindamycin or TMP-SMX ± rifampicin	16/16 (100 %)
[63]	Age of ≥ 5 years (78 %)	36	Osteomyelitis: 36, septic arthritis: 12	36 (100 %)	4/36 (11 %)	NR	NR	NR	36/36 (100 %)

Table 2 (continued)

Reference	Patient age (years)[a]	No of patients	Location of the infection	Bacteremia	DVT	Presence of PVL	MRSA clone	used antibiotics after cultures	Survival
[20]	5.5 years (median) (0.3–17.9)	16	Septic arthritis	NR	NR	14/16(87.5 %)	USA300 13/16 (81.3 %)	NR	16/16 (100 %)
[76]	7.1(3.2–11.5)	44	Osteomyelitis: 33 (75), septic arthritis: 7 (15.9), both: 4 (9.1)	NR	7 (16.3 %)	NR	NR	NR	44/44 (100 %)

DVT deep vein thrombosis, *IV* intravenously, *MRSA* methicillin-resistant *S. aureus*, *NR* not reported, *PO* per os, *PVL* Panton–Valentine leukocidin, *SCC* staphylococcal cassette chromosome

[a] Age is presented in years unless otherwise stated

[b] Healthcare-associated infections were also included

[c] In 2 available isolates

reported, one of which was finally cured, and the other resulted in chronic osteomyelitis. Local complications at the end of treatment included pathological fractures in 7 patients and chronic osteomyelitis in 3.

Case series of CA-MRSA bone/joint infections

We identified 33 case series that included 510 patients with CA-MRSA bone and joint infections [16, 18, 20–23, 26, 28–30, 32–35, 37, 43, 49, 50, 53, 58–60, 63, 64, 69, 70, 72, 74–79]. The majority of the case series included described patients with bone and joint infections due to several pathogens and also included patients with MRSA osteoarticular infections. Therefore, specific data regarding patients with MRSA infections were limited (Table 2). Most of the studies included were performed on children (488 out of 510 patients, 96 %) [16, 18, 20–23, 26, 29, 30, 32–35, 37, 49, 50, 58–60, 63, 64, 69, 70, 72, 76–79], and only 5 included adults [28, 43, 53, 74, 75]. In studies that provided data, bacteremia was present in most of the patients (45–100 %) [18, 21, 22, 34, 35, 49, 50, 59, 60, 63, 72], while DVT was the major complication in 6 of them (4 % in the largest study that provided data [16], up to 100 % in small case series [22, 26, 34, 35, 49, 59, 63, 72, 76]. PVL was present in 166 out of 172 (97 %) of isolates in which it was tested. SCCmec IV USA300 was the predominant clone in the few studies that provided relevant data. One study from France reported that the European clone ST 80 was isolated. Surgical interventions were required in 202 out of 236 (86 %) of patients for whom data were available. Vancomycin and clindamycin were the most commonly prescribed antibiotics. Four patients died (4 out of 370, 1 %) and 16 out of 126 (13 %) developed chronic osteomyelitis.

Discussion

There are limited data regarding the annual incidence of CA-MRSA bone and joint infections. The available evidence shows that it varies according to the location and age of the studied population. Thus, the incidence of invasive CA-MRSA ranged from 1.6 to 29.7 cases per 100,000, while bone and joint infections accounted for 2.8 to 43 % of invasive CA-MRSA infections. In addition, surveillance studies showed that these infections affect mainly patients <2 years of age; the distribution of infections in other age populations depends on the study site and race. However, it seems that black race is associated with a higher risk of infections than white.

The published evidence from case reports and case series suggested that the majority of patients of CA-MRSA bone and joint infections were cured. A total of seven deaths were reported; 3 in case reports and 4 in case series. On the other

hand, complications were relatively common; abscesses, pyomyositis, DVT, and chronic osteomyelitis were the most common local complications. Although systemic complications were also frequent (39 % in case reports), this did not seem to affect mortality. As expected, prolonged antibiotic treatment and hospitalization were employed in most of the cases.

Vancomycin was the most frequently used antibiotic in both case reports and case series. However, clindamycin monotherapy was also used effectively in case series as well as in combination with or following initial vancomycin treatment [16, 49, 50, 69, 72]. In these case series, inducible resistance to clindamycin was not detected. Vancomycin is the treatment of choice for MRSA bone and joint infections [81, 82]. However, specific data regarding the most effective treatment option for CA-MRSA infections are not available. Linezolid, teicoplanin, and daptomycin are alternative options that have been used effectively for the treatment of MRSA bone and joint infections [83–87].

S. aureus is the most commonly isolated pathogen from bone and joint infections [4, 7, 81, 82]. During the last decade, several studies showed that *S. aureus* infections increased, and the relative frequency of MRSA increase was more prominent than that of methicillin-susceptible *S. aureus* (MSSA), both in the community and in hospitals [88–90]. Therefore, it seems prudent to include in the empirical antibiotic regimen a drug that is effective against MRSA. In the limited available data in this review, approximately 50 % of patients did not receive appropriate empirical treatment. Fortunately, this did not seem to have an impact on mortality. However, complications were frequent. Owing to the limited data available, we were unable to identify whether or not the use of appropriate treatment could be associated with fewer complications. A recent review reported that MRSA osteomyelitis in children was associated with more DVTs than MSSA osteomyelitis [91].

Most of the patients included in the present review did not have risk factors for CA-MRSA infection, in accordance with previously published studies [92, 93]. Moreover, a site of entry was not identified, suggesting a hematogenous shedding of MRSA. Hematogenous osteomyelitis of long bones is most commonly seen in children, as was the case in this review. In addition, the propensity of CA-MRSA toward younger individuals has been confirmed in this review. The great majority in both case reports and case series were children. On the contrary, we have previously reported that the majority of published cases of CA-MRSA pneumonia were young adults [92, 93]. Other differences between the two reports included the higher severity of complications and mortality reported in patients with pneumonia.

One study provided data for 5 patients with CA-MRSA prosthetic joint infections [43]. All infections developed early after joint replacement. All patients required replacement of the affected joint and prolonged antibiotic therapy. The isolated strains had identical antibiograms. Molecular characterization of two of them revealed a PFGE type that was identical to the USA300 clone, SCCmec type IV. This report provides further evidence that "community-associated" strains have been identified as a cause of healthcare-associated or hospital-associated infections [94–96].

In conclusion, the currently limited available evidence from case reports and studies with different study designs and patients' characteristics suggests that the incidence of bone and joint infections caused by CA-MRSA varies and depends on the geographic region (even within the same country), age, and race of the population. A propensity toward younger individuals is evident. The currently available treatment options seem to be adequately effective. However, the increase in the number of CA-MRSA infections both in the community and in the hospital among patients with no known risk factors requires increased awareness for early recognition and treatment.

Funding None

Conflict of interest None

Ethical approval Not required

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