Severe community-acquired infection caused by methicillin-resistant *Staphylococcus aureus* in Saudi Arabian children

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ABSTRACT

أصبح ميكروب المكورة العنقودية الذهبية (CA–MRSA) المقاومة لعقار الميثيللين والمكتسبة من المجتمع خارج المستشفى سببا مهما للالتهابات عند الأطفال السعوديون. لقد ظهر هذا الميكروب كمسبب شائع لالتهابات الجلد والأنسجة الرخوة و التي قد يصاحبها التهابات تهدد حياة المريض كالالتهاب الرئوي النخري وتسمم الدم. خلال الفترة من يناير2005 حتى مارس 2008 ووجد أن 5 (6%) من مجموع 80 طفل مصابين بالتهابات المكورة العنقودية (CA–MRSA) المقاومة لعقار الميثيللين والمكتسبة من المجتمع تم تشخيصهم كحالات خطيرة. ثلاثة من هؤلاء الأطفال كانوا مصابين بالتهاب العظام، أحدهم تطور عنده الالتهاب ليشمل الأنسجة الرخوة والأنسجة العظمية محدثا تهتكا شديدا فيهما مما أدى إلى جلطة في الأوعية الداخلية ولاحقا إلى هشاشة وكسر في العظم. أما الطفلين الآخرين، فان أحدهم أصيب بالتهاب في الأعضاء الداخلية والأخر كان رضيعا أصيب بالتهاب خطير في الأنسجة الخارجية للعين وخراج في كلتا العينين وتحت الأنسجة المحيطة بالمخ. تراوح متوسط العمر 4 سنوات بين 3 شهور إلى 17 عام. طفل واحد من هؤلاء كان لديه عامل محفز للالتهاب. تم علاج 2 طفل بداية بمضادات غير فعاله ضد الميكروب (بيتا لاكتام). أظهرت أحد العثرات المعزولة مقاومة لمضاد الكلنداميسين. تماثل جميع الأطفال للشفاء بعد علاجهم بالمضادات المناسبة. نأمل أن يؤدي عرض هذه الحالات إلى مزيد من التوعية لدى الأطباء بشأن الالتهابات الخطيرة التي يسببها هذا الميكروب ويوضح التحدي عند اختيار العلاج المناسب.

Community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infection has become a major pathogen causing significant infection in children in Saudi Arabia. It has emerged as a frequent cause of skin and soft tissue infections and can be associated with life-threatening complications such as necrotizing pneumonia and sepsis. Between January 2005 and March 2008, 5 (6%) previously healthy children with invasive CA-MRSA infections were identified from 80 children with community-onset MRSA infections. Three children had osteomyelitis, with one patient presenting a fulminant and extensive soft tissue and bone destruction complicated by deep vein thrombosis and pathological fracture. One child had deep-seated infection, and one infant had severe orbital cellulitis and bilateral orbital abscess complicated by subdural empyema. The median age was 4-years (range 3 months to 17 years). Only one patient had a risk factor. Two patients were initially treated with ineffective antimicrobial therapy (beta-lactam). One isolate showed inducible clindamycin resistance. The recovery was uneventful in all patients. This report should increase the awareness of clinicians regarding severe CA-MRSA infections and highlight the challenges encountered in the choice of therapy of serious infections caused by this organism.

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Community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is increasingly reported in association with invasive infections such as sepsis, necrotizing fasciitis, necrotizing pneumonitis, and osteomyelitis with deep venous thrombosis (DVT).[1-4] Most CA-MRSA strains contain the virulence factor Panton-Valentine leukocidin (PVL).[5] This virulence factor is rarely found in hospital-acquired MRSA strains or methicillin-sensitive *Staphylococcus aureus* (MSSA) strains, and has been associated with necrotizing pneumonia and death.[6] There is little data on CA-MRSA infection in Saudi children. Bukharie-Huda et al[6] reported that CA-MRSA accounted for 33% (15/45) of the total MRSA cases from King Fahad Hospital, 40% of them were younger than 18 years of age. Reports from the United States (USA) suggest that MRSA accounts

for 76% of all community acquired *Staphylococcus aureus (S. aureus)* isolates in some pediatric centers.[7] We conducted this retrospective review to delineate the disease spectrum and clinical outcome in children with invasive CA-MRSA at King Khalid University Hospital (KKUH), Riyadh, Kingdom of Saudi Arabia, a tertiary care university hospital with a total of 220 pediatrics beds.

Between January 2005 and March 2008, children aged 0-18 years with CA-MRSA infection hospitalized at KKUH, were identified retrospectively. In addition, MRSA and MSSA isolates were retrieved from an electronic *S. aureus* database of the microbiology laboratory. This database is maintained for clinical surveillance purposes. The CA-MRSA infection was identified as a child with an MRSA infection before admission, and no history of risk factors (**Table 1**). The medical records of these children were reviewed for clinical, demographic data, and risk for MRSA acquisition. As this is a retrospective review, patient consent was not obtained. Only children with invasive CA-MRSA infections during the 3-year-period were selected. Invasive MRSA disease was defined as infection verified by culture of specimen from sterile sites including bloodstream, bones and joints, central nervous system (CNS), lung, peritoneal cavity, pericardial cavity, and deep-seated soft tissues such as muscles, fascias, orbital cavities, and lymph nodes. A total of 280 patients with community-onset *S. aureus* infections were identified. The CA-MRSA infections were confirmed in 80 (28.6%) children, most of them presented with skin and soft tissue infections. Five (6%) had invasive disease. Brief case summaries of the 5 patients with invasive CA-MRSA infections are described in **Table 1** .

Case Report. *Patient One* (**Table 1**). A 4-year-old previously healthy Pakistani boy presented to the pediatric emergency department with a 4-week history of fever and abdominal distention. On examination, he appeared toxic and his temperature was 40^0C. Abdominal examination revealed palpable mass in the left hypochondrial area. White blood cell (WBC) count was $27x10^9$/L (normal: 5-15.5 g/L) with 63% (normal: 30-35%) neutrophils, hemoglobin 8.6 g/dL (normal: 10.5-13.5 g/dL), and erythrocyte sedimentation rate (ESR) of 119 mm/hour (normal: 3-9

Table 1 - Clinical and laboratory characteristic of community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) cases.

Age	Gender	Origin	Site of Infection	Risk factors*	Treatment	Complication	Outcome
4 years	Male	Pakistani	Iliopsoas abscess (9.4 x 6.2 cm)	None	IV Vancomycin x 3 weeks + PO Rifampin + aspiration drainage	No	Good
18 months	Female	Saudi	Tibial osteomyelitis	None	IV Vancomycin x 3 weeks IV Clindamycin x 6 weeks Oral Clindamycin x 8 months + drainage heparin infusion + warfarin	Left popliteal and posterior tibial veins DVT Pyomyositis of calf and thigh muscles Knee arthritis	Chronic osteomyelitis and pathological fracture L. tibia
3 months	Female	Saudi	Rt. Orbital abscess and cellulitis	None	IV Cefazolin and Gentamicin x 48 hours (empirical) Vancomycin x 6 weeks + abscess drainage	Bilateral orbital abscess, subdural emyema (left temporal lobe abscess)	Good
8 years	Male	Saudi	Osteomyelitis Rt. tibia, distal tibia abscess Rt. ankle arthritis	None	IV Ceftriaxone and Cloxacillin x one week (empirical) IV Clindamycin x 2 weeks PO Clindamycin x 6 weeks + abscess drainage	No	Good
17 years	Male	Saudi	Rt. femur Osteomyelitis and chronic thigh soft tissue osteomyelitis abscess Sinus formation	Rt. femur Chronic osteomyelitis	Debridement of soft tissue and bone IV Vancomycin x 2 weeks PO Clindamycin x 3 months	No	Good

Rt – right, DVT - deep venous thrombosis, IV - intravenous, PO - per os.
*Risk factors: 1) hospitalization within one year, 2) chronic disease (malignancy, congenital heart disease, eczema, prematurity), 3) surgical procedure and MRSA infection or colonization within previous one year

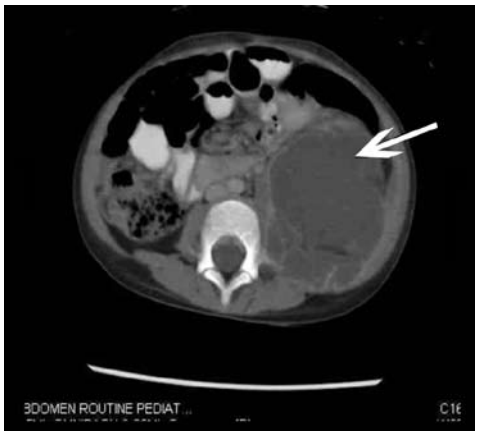

Figure 1 - Abdominal CT scan showed a large (9.4x6.2 cm) iliopsoas abscess involving the posterior abdominal wall (patient one).

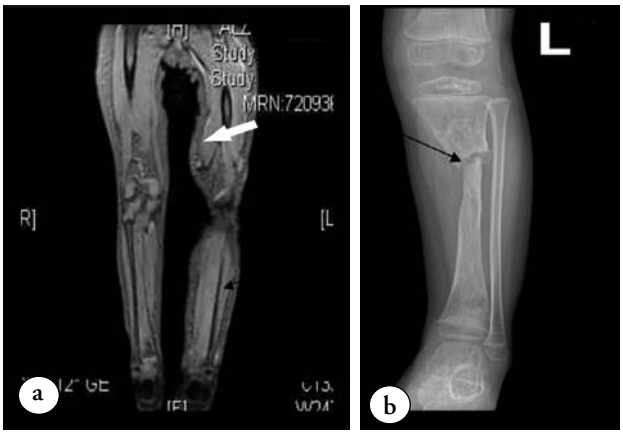

Figure 2 - **a**) Magnetic resonance imaging performed on day 7 after onset of disease revealed extensive inflammation of the calf muscles and soft tissue of the anterio-lateral aspect of the left thigh (patient 2). **b**) X-ray showed pathological fracture in the mid shaft of the tibia 3 months after discharge (patient 2).

mm/hr). Abdominal CT scan revealed a large (9.4x6.2 cm) iliopsoas abscess involving the posterior abdominal wall (**Figure 1**) and extending to the epidural space with displacement of the left kidney. The abscess was drained under CT guidance and approximately 100 mL of pus was aspirated and sent for culture. Culture of pus aspirate revealed pure growth of MRSA. Blood cultures were negative. Treatment was commenced with 40 mg/kg of intravenous vancomycin. As he remained febrile after 7 days of aspiration and antibiotic treatment, rifampin (20/kg/day) was added. Two days later, the fever subsided and repeated WBC and ESR showed normal values. After 3-weeks of combined antibiotic therapy, he was discharged in good condition. On follow up, MRI of the abdomen revealed complete resolution of the psoas muscle abscess.

Patient 2. An 18-month-old girl was admitted with one-day history of fever and inability to bear weight on the left leg. On physical examination, she was febrile with a temperature of 38.5^0C. Limb examination revealed swelling, redness, and marked tenderness over the upper one third of the left leg below the knee joint. A preliminary diagnosis of acute osteomyelitis was made. Laboratory investigations showed a WBC count of $24x10^9$/L with 70% neutrophils, and ESR of 120 mm/hour. Initial radiological examination showed no abnormality. Based on high clinical suspicion of acute osteomyelitis, CT-guided aspiration from the proximal one third of the tibia was performed and pus was sent for culture. Pus and blood cultures grew MRSA. She was started on vancomycin 40mg/kg/day intravenously. On day 7, she developed progressive thigh swelling and high temperature (40^0C). Urgent ultrasound examination revealed sub-acute deep venous thrombosis (DVT) of the left popliteal and posterior tibial veins. Low molecular weight heparin infusion was commenced. After 5 days as the repeated Doppler ultrasound showed resolution of the thrombosis, heparin was discontinued and warfarin was started. On day 10 of admission, left limb MRI revealed extensive inflammation of the calf muscles and soft tissue of the lateral aspect of the left thigh with remarkable left knee effusion and bony changes suggestive of osteomyelitis (**Figure 2a**). She was taken promptly to the operating room for debridement. Fascial necrosis and pus production without visible signs of necrotizing fasciitis were found intra-operatively. Fascia pathology specimens were not consistent with necrotizing fasciitis. Tissue cultures were negative. She underwent extensive wound debridement. Vancomycin was ceased and intravenous clindamycin was started. She completed 6 weeks of clindamycin therapy and showed marked improvement in the soft tissue and muscles of the left leg. She developed chronic osteomyelitis and pathological fracture of the tibia 3 months after discharge (**Figure 2b**).

Patient 3. A 3-month-old girl was referred to our facility with a 10-day history of fever and right eye swelling. Her initial diagnosis was right eye orbital cellulitis with abscess collection unresponsive to intravenous cloxacillin and ampicillin. On admission, she was febrile (39^0C), irritable, and toxic looking. The right eye showed severe proptosis with the eye pushed downward and temporally, with severe eyelid redness and swelling. A small bilateral abscess was noted by trans-illumination on the superior-nasal aspect of the upper lid. Portable slit lamp examination revealed clear anterior segment with no anterior chamber reaction. The pupil was round, regular, and reactive. Fundus examination was not carried out as she was sick. Initial laboratory investigation showed a WBC count of $14.4x10^9$/L,

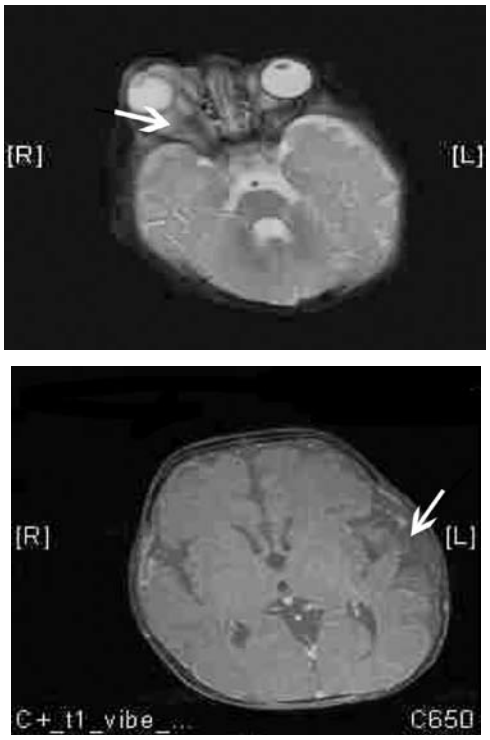

Figure 3 - Magnetic resonance imaging showing the **a)** right orbital abscess with extension through eroded bone into the **b)** left temporal fossa (extradural collection) (patient 3).

and Hb 9.5 g/dl. The ESR was 110 mm/hour. Blood culture was negative. Urgent MRI of the orbit and brain revealed a bilateral orbital abscess involving mainly the right eye with extension through eroded bone into the left temporal fossa with extradural collection (**Figures 3a & 3b**). Lumbar puncture was carried out for CSF analysis and culture. The CSF was turbid and the WBC count was 2400/mm^3 with 95% polymorphonuclear leukocytes. She was started empirically on cefazolin and gentamicin. She then underwent incision and drainage of the abscess through the medial side of the right eye by an oculoplastic surgeon. The drained pus was sent for Gram-stain and culture. Microscopic examination of the CSF and pus showed Gram-positive cocci in clusters, and the culture grew MRSA after 48 hours of incubation. Accordingly, she was treated with intravenous vancomycin 40mg/kg/day for 6 weeks. She showed remarkable improvement in her eye swelling, movement, and shape. Repeated eye and brain MRI demonstrated normal orbit with resolution of the extradural collection.

Patient 4. An 8-year-old Saudi boy presented to the pediatric emergency department with a 7-day-history of fever and inability to bear weight on his right foot. Examination revealed an irritable boy with temperature of 38.9^{0}C. He had diffuse swelling of his right ankle with tenderness over the distal end of the tibia. Laboratory investigations showed a WBC was 11.2x10^9/L with 72% neutrophils, and ESR of 98 mm/hour. Right ankle x-ray showed only soft tissue swelling. He was commenced empirically on intravenous ceftriaxone and cloxacillin. His condition worsened with continuing fever, gross swelling, and tenderness of the right ankle. Right-leg MRI revealed findings suggestive of septic arthritis of the right ankle joint and osteomyelitis of the distal end of the right tibia. The boy required surgical drainage and arthrotomy of his right ankle. An abscess near the distal tibia, necrotic tissue, and purulence within the ankle joint were noted. Pus was drained and sent for culture, which grew MRSA. The patient was started on intravenous clindamycin 40 mg/kg/day and continued on oral clindamycin for 6 weeks. Five months later he had recovered well without any obvious adverse sequelae.

Patient 5. A 17-year-old boy presented with fever, progressive pain, and swelling over the right thigh 2 weeks before admission. In 2001, he was diagnosed to have chronic right femur osteomyelitis treated by multiple surgical debridement and antibiotics. On admission, he was febrile (38^{0}C). Local examination revealed swelling and tenderness of the right thigh. Discharge of pus from a sinus on the back of the right thigh was noted. Other physical examination was unremarkable. The WBC count was 13x10^9/L with 85% neutrophils, ESR of 70 mm/hour, and C-reactive protein (CRP) 209 mg/L. Hip x-ray showed deformed femur. An MRI revealed pus collection in the femur and around the thigh muscles. Operative debridement was performed 24 hours after admission for progression of infection. Culture of tissue specimens yielded MRSA. Vancomycin was started for a 2-week course. He was discharged on oral clindamycin for 3-months, with follow up in the orthopedic clinic.

Microbiological data. Methicillin resistance was determined by minimum inhibitory concentration using the Microscan broth culture system (Siemens Healthcare Diagnostics, Camberley, United Kingdom) and confirmed with the disk diffusion methods and interpretation guidelines of the Clinical and Laboratory Standards Institute (CLSI). Double-disk diffusion tests (D-tests) were performed to determine inducible clindamycin resistance. The 5 MRSA isolates had similar antibiotic susceptibility patterns, with resistance to oxacillin and susceptibility to erythromycin, clindamycin, ciprofloxacin, rifampin, vancomycin, trimethoprim-sulfamethoxazole, and linezolid. Deviation from this susceptibility pattern was observed in one isolate (Patient one) with resistance to erythromycin and positive D-test (inducible clindamycin resistance). The isolates were not obtainable for molecular characterization.

Discussion. We have described clinical manifestations of 5 severe pediatric cases of CA-MRSA infection. Common clinical disease entities included osteomyelitis/arthritis with or without DVT. Deep-seated abscess, pyomyositis, and invasive CNS involvement were also demonstrated. There are several published reports of severe CA-MRSA infections worldwide.[2,8] In Saudi Arabia, most reported cases were minor infections involving mainly the skin and soft tissue.[6] In a review of 58 cases of *S. aureus* infections requiring admission to a pediatric intensive care unit in New Zealand,[9] 95% were community acquired and 12% were methicillin resistant. The CA-MRSA strains are virulent, are typically sensitive to antimicrobials other than beta lactams, and strongly associated with skin and soft tissue suppuration. The 5 cases described here, illustrate the potential virulence of CA-MRSA. Three patients presented with features of osteomyelitis with rapid progression in one patient and development of DVT and pyomyositis. Deep venous thrombosis has been increasingly observed in children in association with osteomyelitis due to *S. aureus* containing the PVL genes.[10] The combination of acute osteomyelitis, DVT, and pneumonia has been observed in adults and children in association with PVL-positive *S. aureus.*[11] This multifocal infection is life threatening and requires aggressive management with antibiotics, anti-coagulation therapy, and surgical drainage. There are minimal data on molecular characteristics and type of prevalent MRSA strains in Saudi community. In a recent study, Moussa and Shibl[12] described the molecular characterization of MRSA recovered from outpatient clinics in our facility, only 3 strains 3/37 (8.1%) isolated from skin and soft tissue infections were positive for PVL and SCCmec type IV. The percentage of CA-MRSA obtained in this study indicated that there is an increase in the number of patients with CA-MRSA in the Kingdom of Saudi Arabia. Further studies to determine CA-MRSA strains carrying PVL in the Saudi community are warranted. Pneumonia caused by CA-MRSA is uncommon, but potentially serious. However, we did not identify any pulmonary involvement with or without musculoskeletal infections in the past 3 years. Among the reported pediatric invasive CA-MRSA infections in Taiwanese children,[13] 18/31 (58.1%) children had bone/joint infections. The lower limbs were the most commonly affected sites and included the hip joint in 10 (55.6%), femur in 5 (27.8%), tibia in 3 (16.7%), and fibula in one (5.6%). Deep-seated soft tissue infections including pyomyositis and necrotizing fasciitis involving predominantly the lower limbs and abdomen were identified in 45.2% in the same study. Surgical interventions and drainage of the deep-seated abscesses are usually required for full recovery. In this report, the outcome was uneventful in all, but one who had chronic osteomyelitis and pathological fracture.

Ophthalmic manifestations of infections caused by CA-MRSA have been described. Rutar et al[14] reported 9 patients with CA-MRSA infections of the eye and orbit identified at 2 hospitals in San Francisco. The infections included orbital cellulitis, endophthalmitis, panophthalmitis, lid abscesses, and septic venous thrombosis. All but one patient had good visual outcomes, with the later deteriorating to no light perception. The 3-month-old infant reported in this series presented with progressive orbital cellulitis with extradural extension involving the right temporal fossa. She was initially treated with cefazolin and gentamicin without a clinical response. The delayed use of effective antibiotics may contribute to serious complications and death.[9] Vancomycin is recommended for life-threatening infections suspected to be MRSA.[10] Three of our reported patients received vancomycin therapy as an initial treatment. Clindamycin is active against MSSA and most strains of CA-MRSA. However, clindamycin and lincomycin are bacteriostatic agents and are not recommended as monotherapy of severe staphylococcal sepsis. In addition, D-test should be performed prior to clindamycin therapy for erythromycin resistant isolates to detect clindamycin inducible resistance with potential treatment failure.[15] Linezolid and daptomycin are alternative medications. Recent reports have shown the efficacy of linezolid in the treatment of patients with CNS infections.[16] Surgical drainage of abscesses should be performed in combination with antibiotics. In fact, surgical drainage was found in some studies to be the most important management of patients with CA-MRSA infections.[7,17]

In conclusion, during our retrospective review over 3 years, only 5 cases (5/80) of invasive CA-MRSA infections were identified without reported deaths. All cases required some form of drainage and 2 of 5 cases did not receive appropriate antibiotic coverage for MRSA. Pediatricians and microbiologists need to be aware of the spectrum of infections caused by CA-MRSA for early recognition of life-threatening infections and prompt use of effective antibiotics.

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