Brief Original Article

Community-associated methicillin-resistant *Staphylococcus aureus* infections in a pediatric intensive care unit

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Abstract

Introduction: Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infection is an increasing problem worldwide. In developing countries, there is little data on CA-MRSA infection in children. This study reviewed the clinical features and outcomes of children admitted in a Tunisian pediatric intensive care unit with severe CA-MRSA infections.

Methodology: Retrospective chart review of patients coded for CA-MRSA over 10 years.

Results: There were 14 (0.32% of all admissions) patients identified with severe CA-MRSA infections. The median age was three months (range, 0.5–156 months). All patients had pulmonary involvement. Six children (42.8%) developed septic shock. Two (14.3%) patients had multifocal infection with deep venous thrombosis. Two (14.3%) patients died.

Conclusions: Severe CA-MRSA pneumonia dominated presentation. The mortality of CA-MRSA infection in our series is lower than that previously reported.

Key words: methicillin-resistant *Staphylococcus aureus*; severe sepsis; pediatric intensive care unit; necrotizing pneumonia

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Introduction

Staphylococcus aureus is a frequent cause of infections in children, ranging from skin and soft tissue to invasive life-threatening infections [1]. Although community-associated methicillin-resistant *S. aureus* (CA-MRSA) isolates often are resistant only to methicillin and usually associated with skin and soft tissue infection, CA-MRSA isolates may also cause invasive and severe infections and even death in apparently healthy pediatric patients [2,3]. CA-MRSA infection in children is an increasing problem worldwide [4-8]. There is little published data on CA-MRSA infection in Tunisian children but reports from the United States suggest that MRSA accounts for up to 76% of all community-associated *S.* aureus isolates in some pediatric centers [5]. Children with severe CA-MRSA presenting to the pediatric intensive care unit (PICU) tend to develop multisystemic disease, either by direct invasion or toxin production, before the diagnosis is made and treatment initiated [9]. There is limited literature, with only single case reports or small patient groups, describing CA-MRSA in children admitted to an intensive care unit in the developed world [8, 10-11]. There have been no previous studies of CA-MRSA in children admitted in PICU in a developing country. This study evaluates the clinical features and mortality from CA-MRSA in those children who require intensive care management in a developing country.

Methodology

A retrospective review of clinical notes from all children with CA-MRSA admitted from 1 January 2000 to 31 December 2009 to a PICU was undertaken. The PICU is in a university affiliated children's hospital and provides intensive care services to a national pediatric population of 850,000 children younger than 15 years old. The hospital has 360 beds and the PICU has 14 beds. There were 4273 children admitted to the PICU during the study period. Neonates were only included if admitted to the PICU from the community. Children coded for MRSA were identified from the PICU database. All clinical notes were reviewed by one investigator using a standardized questionnaire that sought

information on patient demographics, clinical findings, investigations, microbiology, and management in the PICU. Cases were included if blood or an isolate from a site that is normally sterile was positive for MRSA and/or the infection was community-associated. Community-acquired infection was defined by an isolate obtained within 48 hours of admission [5]. A severity of illness score (Pediatric Risk of Mortality Score PRISM) [12] was calculated for each patient. PRISM is a tool which uses 14 physiological variables measured at first contact with intensive care to assess severity of illness and give an index of risk of mortality for a population of children [12].

Results

Between 1 January 2000 and 31 December 2009, ninety-four patients with severe *Staphylococcus aureus* infection were admitted to the PICU of the Children's Hospital of Tunis; 14 (14.9%) met the inclusion criteria. These 14 children accounted for 0.32% of the 4,273 admissions to the PICU over the study period. Table 1 shows their demographics and outcome data. More than fifty per cent (56.4%) of the PICU admissions for CA-MRSA happened during 2008 and 2009, and 71.4% of hospitalizations occurred outside of the normal influenza season, which extends from November to March in Tunisia.

The median age of infection was three months (range, 0.5-156 months) with a predominance of infants under three months (57%). Males accounted for five cases (35.7%). The median PRISM was 12, with a predicted mortality rate of 8.5%. The observed mortality rate was 14.3% (2 of 14), compared with an overall PICU mortality rate during the study period of 16%. The mean PICU stay of severe CA-MRSA cases was 14 days (range, one to 39 days), compared with our overall average PICU stay of 7.9 days. All children were transferred to the PICU following clinical deterioration on the ward after a mean delay of 2.9 ± 2.3 days (range: one to seven days). Reasons for ICU admission were respiratory failure requiring ventilation (71.4%) and septic shock (28.6 %), although several children required multiple interventions.

All children had pulmonary involvement. Eleven

Table 1: Severe CA-MRSA Infections in PICU: Epidemiologic data

Case/month and year of admission	Age (months)/sex	PRISM	Infected site culture (+)	Antibiotic treatment	Ventilation/Inotrope (days)	PICU (days)	Outcome
1/09-2009	9/M	8	Lung	Teicoplanin	2	4	Survived
2/09-2009	157/M	18	Bld/joint	Vanc/Gent	8/2	9	Died-refractory shock
3/12-2008	7/F		Lung	Vanc/Gent	20/4	29	Survived
4/09-2008	5/M		Bld	Fosf/Ctx/Gent	1/1	1	Died-refractory shock
5/06-2006	.5/F		Lung/Bld	Fosf/Ctx/Gent	9/5	15	Survived
6/11-2001	3.5/F	18	Bld/CSF	Fosf/Ctx/Gent	2	39	Survived
7/09-2008	2/F	13	Lung	Teicoplanin	10	11	Survived
8/10-2006	2/F	33	Lung	Fosf/Ctx/Gent	5/2	18	Survived
9/09-2003	16/F	5	Lung	Fosf/Ctx/Gent	12	26	Survived
10/09-2008	21/F	12	Lung	Fosf/Ctx/Gent	1	3	Survived
11/10-2008	1/F	5	Lung	Teicoplanin	5	7	Survived
12/12-2007	3/M	9	Lung/Bld	Vanc/Gent	1	8	Survived
13/12-2007	3/M	15	Lung	Vanc/Gent	15	18	Survived
14/04-2001	11/F	3	Lung	Fosf/Ctx/Gent	16	9	Survived

M, male; F, female; Bld, blood; Vanc, vancomycin; gent, gentamicin; fosf, fosfomycin; Ctx, cefotaxime; CA-MRSA, community-acquired methicillin resistant *Staphylocoocus aureus* PICU, pediatric intensive care unit; PRISM, Pediatric Risk of Mortality score.

(78.6%) had pneumonia on chest radiographs. Pleural drains were required in 13 of 14 children with empyema (n = 4), pyopneumothorax (n = 4), or pneumothorax (n = 5). Pleural drains were unilateral in nine patients and bilateral in four patients. All children required ventilation for a mean of 7.64 (SD 6.28, range: 1-20) days.

Six children (42.8%) developed septic shock (defined as inadequate tissue perfusion from sepsis despite adequate filling) and five required inotropic with vasopressor support (dobutamine 10-20 µg/kg/min, noradrenaline 0.5-4 µg/kg/min). The mean duration of inotrope and vasopressor support was 2.8 (SD 1.6, range: 0 - 5) days. The initial white blood cell count ranged from 1600/mm3 to 35 000/mm3. Five patients were leukopenic on admission, one of whom died. All patients had elevated C-reactive protein (mean: 198.32 ± 103.56 mg/L, range: 55-484), and the mean platelet count was 484428/mm3 (range: 16000-1124000 /mm3). Hyponatremia (< 130 mmol/L) was a common feature encountered in nine (64.3%) patients (mean: 123 ± 6.52 mmol/L, range: 112-128). Renal failure occurred in one patient, who had not required renal dialysis. A coagulopathy was seen in one child on presentation, and six progressed to multisystem organ failure. Of the 14 children, two (14.3%) had multifocal infection.

One child aged 13 years had multiple joint involvement with three sites affected simultaneously (right knee, elbow, and left wrist) and required surgical drainage. The right knee septic arthritis was complicated by a femoral vein thrombosis with bilateral nodular densities consistent with septic emboli seen on chest radiographs.

Another child initially developed a preseptal cellulitis which was complicated by MRSA bacteremia, zygomatic bone osteomyelitis, cavernous septic thrombosis, meningitis and septic pulmonary localization. Blood culture was positive for MRSA in five children, with blood culture alone in two children. The content of thoracocentesis fluid grew MRSA in eleven patients; four grew MRSA from tracheal aspirates, and MRSA was isolated from either CSF or joint aspirate in two additional cases. The initial antibiotic started on admission to either the PICU or to hospital was inappropriate in 11 (78.6%) children. The initial antibiotic was ceftriaxone in five children, flucloxacillin in four children, and amoxicillin-clavulanic acid in two children. The treatment regime for these children was changed, based on culture and susceptibility results to the combination of fosfomycin, cefotaxime and gentamicin in seven cases, vancomycin and gentamicin in four cases, and teicoplanin in three cases. Eight children received antibiotics for more than 15 days with a mean duration of 18.4 ± 11.28 days (range: 15-42 days). It was not possible to determine duration of antibiotics in six children who were transferred to other hospitals after PICU discharge. The MRSA isolates from these patients had a similar antibiotic susceptibility pattern: all were susceptible by disk diffusion to vancomycin, fosfomycin, gentamicin, and trimethoprim-sulfamethoxazole. Only two MRSA isolates showed clindamycin resistance and four MRSA isolates were resistant to erythromycin.

Discussion

Our results, collected over 10 years from a single institution, differ significantly from prior literature reports of severe CA-MRSA infection in children. The main differences include: substantially lower mortality (14.3% compared to the range of 30-50% previously published [11,13]), and a younger population (median age of three months versus 13-14 years in previous reports [11,14]), the predominance of the pulmonary involvement, and the rarity of musculoskeletal disease.

The most likely explanation of the differences from other published series is the case definition. We specifically used the criteria available in usual clinical practice, the antibiotic susceptibility pattern, to define our cases. Antibiotic susceptibility patterns also do not necessarily predict whether the isolate is a Panton-Valentine leukocidin (PVL)-producing strain [15]. PVL production varies significantly among different clinical isolates [16], suggesting other factors affect the phenotype and therefore the need for ICU care. While debate continues regarding whether the PVL toxin is the most important virulence factor [17,18], presence of PVL appears to be an efficient marker for the more virulent strains [13]. The majority of our patients had lung necrosis and/or rapidly progressive pleural effusions. Since deterioration occurred when patients did not receive an antibiotic known to inhibit exotoxin production [19], antibiotic resistance patterns did clinically select patients with a high probability of toxin-producing CA-MRSA strains. However, the present study lacks molecular genetic analysis of the strains to support this hypothesis.

The lower mortality found in our study has three possible explanations. The first is again case

definition. A previously published case series focused on cases accumulated by a center with specialized research interest in PVL-producing CA-MRSA [13]. The case series of Gillet *et al*. included 50 cases over nine years from 32 hospitals in nine countries, suggesting a significant selection bias [13]. A second possible explanation is the lack of seasonal variation (71.4% occurred out of the flu season), suggesting that antecedent influenza was not a necessary feature of CA-MRSA pneumonia. In contrast, previous studies have suggested a significant relationship between lethal CA-MRSA pneumonia and preceding influenza [20,21]. Indeed, the interaction between influenza and CA-MRSA may either result in a highly lethal combination with unique clinical features or may stem from a more susceptible host genetic predisposition [22]. Unfortunately, this study lacks virological investigation to support either hypothesis. The last possible explanation for the mortality divergence is differences in treatment. Half of our patients (7/14) had received an empirical combination of parenteral fosfomycin, cefotaxime and gentamicin that achieved reasonable pulmonary, bone and brain penetration and was empirically active against *S. aureus* (including CA-MRSA strains). Fosfomycin, by inhibiting the production of penicillin binding protein PBP2a, which is involved in methicillin-resistance, restores the susceptibility of the MRSA strains to cefotaxime. This association allows rapid and total eradication even in the presence of a high bacterial inoculum. Finally, the rarity of musculoskeletal infections in this case series (2/14) contributes to the better prognosis since more severe complications such as deep venous thrombosis are seen in patients with musculoskeletal infections caused by CA-*S. aureus* isolates, particularly when carrying the PVL genes [23]. Our patients with CA-MRSA infection also did not have risk factors: none had concurrent skin lesions and all were immunocompetent.

In conclusion, despite necrotizing features, we found that the mortality due to CA-MRSA infection in our study populations was not as high as reported in other studies. Our treatment strategy may explain this better outcome. CA-MRSA is not necessarily a post-influenza infection. No clinical factors are highly predictive of CA-MRSA but suspicion should be raised by the radiographic features of necrotizing pneumonia and rapidly increasing pleural effusions. The increasing penetration of CA-MRSA in the community requires the dissemination of information to primary care providers about the potential severity of this infection, methods for rapid and accurate diagnosis, and the need to rapidly implement appropriate empiric and definitive treatment regimens.

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