Community-acquired methicillin-resistant Staphylococcus aureus infections requiring admission to a Tunisian paediatric intensive care unit

Khaled Menif, Asma Bouziri, Ammar Khaldi, Asma Hamdi, Sarra Belhadj, Aida Borgi, Najla Ben Jaballah

Pediatric intensive care unit, children's hospital of Tunis –Tunisia
Tunis El Manar University

K. Menif, A. Bouziri, A. Khaldi, A. Hamdi, S. Belhadj, A. Borgi, N. Ben Jaballah

Infection communautaire à Staphylocoque aureus résistant à la méthicilline nécessitant l'admission en réanimation pédiatrique en Tunisie

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RÉSUMÉ

Prérequis: Les études antérieures concernant les infections communautaires sévères à Staphylocoque aureus résistant à la méthicilline (SARM) chez l'enfant sont rares.
But : Préciser les caractéristiques cliniques et le devenir d'enfants admis en réanimation pédiatrique en Tunisie pour infection communautaire sévère à SARM.
Méthodes : revue rétrospective des observations médicales des patients codés infection communautaire à SARM sur une période de 10 ans.
Résultats : Quatorze patients (0.32 % de toutes les admissions) ont été identifiés infection communautaire sévère à SARM. Leur âge médian était de 3 mois (extrêmes: 0.5 - 156 mois). Tous les patients présentaient une localisation pulmonaire. Six enfants (42.8 %) ont développé un choc septique. Deux patients (14.3 %) présentaient une infection multifocale avec une thrombose veineuse profonde. Deux patients (14.3 %) sont décédés.
Conclusion : La pneumonie communautaire sévère à SARM a dominé les présentations cliniques. La mortalité de l'infection communautaire à SARM dans notre série est inférieure à celle rapportée dans la littérature.

Mots-clés

CAMRSA; sepsis sévère; service de réanimation pédiatrique; pneumonie nécrosante.

SUMMARY

Background: There is limited literature describing severe community acquired methicillin-resistant S aureus (CA-MRSA) in children admitted to an intensive care unit.
Aim: To review clinical features and outcome of children admitted in a Tunisian pediatric intensive care with CA-MRSA.
Methods: 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. The median age was 3 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.
Conclusion : Severe CA-MRSA pneumonia dominated presentation. The mortality of CA-MRSA infection in our series is lower than reported in the literature.

Key-words

CAMRSA; severe sepsis; pediatric intensive care unit; necrotizing pneumonia

S*taphylococcus aureus* is a frequent cause of infections in children, ranging from skin and soft tissue to invasive life-threatening infections [1]. Although community acquired 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 deaths in apparently healthy pediatric patients [2, 3]. CA-MRSA infection in children is an increasing problem worldwide [4–8].

There are little data on CA-MRSA infection in Tunisian children but reports from the USA suggest that MRSA accounts for up to 76% of all community acquired *S. aureus* isolates in some pediatric centers [5]. Children with severe CA-MRSA presenting to the pediatric intensive care unit (PICU) tend to have multisystemic disease, either by direct invasion or toxin production, before the diagnosis is made and treatment instigated [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 developed world [8, 10-11]. There have been no previous studies of CA-MRSA in children admitted in PICU in 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.

MATERIAL AND METHODS

A retrospective review of clinical notes from all children with CA-MRSA admitted from January 1, 2000 and December 31, 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 less than 15 years old. The hospital has 36**0** 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 if the infection was acquired in community. Community acquired infection was defined by an isolate obtained within 48 hours of admission. 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 January 1, 2000 and December 31, 2009, 94 patients with severe *Staphylococcus aureus* infection were admitted to our PICU; 14 (14.9%) responded to the inclusion criteria. These 14 children accounted for 0.32% of the 4273 admissions to PICU over the study period. Table 1 shows their demographics and outcome data. More than fifty per cent (56.4%) of PICU admissions for CA-MRSA happened on years 2008 and 2009. Besides 71.4% of hospitalization occurred out of flu season which usually extends in Tunisia from November to March. The median age was 3 months (range, 0.5–156 months) with predominance of infant under 3 months (57%). Males accounted for 5 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 was 14 days (range, 1–39 days), compared with our 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, 1-7 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 (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 9 patients and bilateral in 4 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 5 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, and 1 of them died. All patients had elevated C-reactive proteins (mean: 198.32±103.56 mg/L range 55-484). Mean platelet count was 484428/mm3 (range: 16000-1124000 /mm3). Hyponatremia (<130mmol/L) was a common feature encountered in 9 (64.3%) patients (mean: 123±6.52mmol/L range 112-128). Renal failure occurred in one patient, who had not required renal dialysis. A coagulopathy was seen in 1 child on presentation; and 6 progressed to multisystem organ failure.

Of the 14 children, 2 (14.3%) had multifocal infection. One children aged of 13 years had multiple joints involved with 3 sites affected simultaneously (right knee, and elbow and left wrist) which 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.

The second children had developed initially 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 5 children. The content of thoracocentesis fluid grew MRSA in 11 patients and four patients grew MRSA from tracheal aspirates. MRSA was isolated from CSF in one patient and from joint aspirate in another patient. 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 5 children, flucloxacillin in 4 children and Amoxicillin- Clavulanic Acid in 2 children. These antibiotics treatment were changed based on susceptibility test to the combination of fosfomycin, cefotaxim and aminosid in 7 cases, vancomycin and aminosid in 4 cases and teicoplanin in 3 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 6 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 teicoplanin, 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 30-50% previously published [11, 13], and younger population (median age of 3 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 sensitivity 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].

In addition, PVL production varies significantly among different clinical isolates [16], suggesting other factors affects 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]. Since the majority of our patients had lung necrosis and/or rapidly progressive pleural effusions and 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.

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. Previous case series were cases accumulated by a center with specialized research interest in PVL-producing CA-MRSA [13]. The case series of Gillet et al accumulated their 50 cases over 9 years from 32 hospitals in 9 countries, suggesting a significant selection bias [13]. Another possible explanation is the lack of seasonal variation (71.4% occurred out of the flu season) that suggests that antecedent influenza is not a necessary feature of CA-MRSA pneumonia. In fact, previous studies have suggested a significant relationship between lethal CA-MRSA pneumonia and preceding influenza [20, 21]. Therefore, the interaction between influenza and CA-MRSA may be a highly lethal combination with unique clinical features or may represent a unique host genetic predisposition [22]. Unfortunately, this study lacks virological investigation to support this 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, cefotaxim and aminosid that will achieve reasonable pulmonary, bone and brain penetration and is likely to be active against *S. aureus* (including CA-MRSA strains).

Fosfomycin by inhibiting the production of penicillin binding protein (PBP2a) involved in methicillinoresistance restore the susceptibility of the MRSA strains to cefotaxim. This association allows rapid total eradication even in 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 are immunocompetent.

CONCLUSION

Despite necrotizing features, we found that the mortality of CA-MRSA is not as high as previously reported. 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 disseminating information to primary care providers about the potential severity of this infection, methods for rapid and accurate diagnosis, and need to rapidly implement appropriate empiric and definitive treatment regimens.

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