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Severe Staphylococcal Sepsis in Adolescents in the Era of Community-Acquired Methicillin-Resistant *Staphylococcus aureus*

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ABSTRACT. *Objective.* More than 70% of the community-acquired (CA) staphylococcal infections treated at Texas Children's Hospital are caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Since September 2002, an increase in the number of severely ill patients with *S aureus* infections has occurred. This study provides a clinical description of severely ill adolescent patients and an analysis of their isolates using molecular methods.

Methods. We identified adolescent patients meeting criteria for severe sepsis requiring admission to the PICU. Patient records were reviewed, and isolates were obtained for susceptibility testing and DNA extraction. Isolates were tested for the presence of virulence genes (*cna*, *tst*, *lukS-PV*, and *lukF-PV*) and enterotoxin genes (*sea*, *seb*, *sec*, *sed*, *seh*, and *sej*) by polymerase chain reaction. Genomic fingerprints were determined by repetitive-element polymorphism polymerase chain reaction and pulse-field gel electrophoresis. SCCmec cassette type was determined.

Results. Fourteen adolescents with severe CA *S aureus* infections were identified between August 2002 and January 2004. All were admitted to the PICU with sepsis and coagulopathy. Twelve patients had CA-MRSA infections; 2 had CA methicillin-susceptible *Staphylococcus aureus* (MSSA) infections. The mean age was 12.9 years (range: 10-15 years). Thirteen patients had pulmonary involvement and/or bone and joint infection; 10 patients had ≥ 2 bones or joints infected (range: 2-10); 4 patients developed vascular complications (deep venous thrombosis); and 3 patients died. All isolates were identical or closely related to the previously reported predominant clone in Houston, Texas (multilocus sequence type 8, USA300), and carried *lukS-PV* and *lukF-PV* genes as well as the SCCmec type IVa cassette (12 MRSA isolates) but did not contain *cna* or *tst*. Only 1 strain carried enterotoxin genes (*sed* and *sej*).

Conclusions. Severe staphylococcal infections in previously healthy adolescents without predisposing risk factors have presented more frequently at Texas Children's Hospital since September 2002. CA MRSA and clonally related CA MSSA characterized as USA300 and

sequence type 8 have been isolated from these patients. *Pediatrics* 2005;115:642-648; community-acquired *Staphylococcus aureus*, methicillin-resistant, severe sepsis.

ABBREVIATIONS. CA, community acquired; MRSA, methicillin-resistant *Staphylococcus aureus*; PVL, Pantone-Valentine leukocidin; TCH, Texas Children's Hospital; PCR, polymerase chain reaction; REP-PCR, repetitive-element polymorphism polymerase chain reaction; PFGE, pulse-field gel electrophoresis; MSSA, methicillin-susceptible *Staphylococcus aureus*; ST, sequence type.

Staphylococcus aureus is a frequent cause of infections in children, ranging from skin and soft tissue to invasive life-threatening infections.¹ Although antibiotic therapy has reduced the mortality associated with *S aureus* septicemia from 80% to 20%,² staphylococcal sepsis remains a significant clinical problem, not only for hospital-acquired infections but also for community-acquired (CA) infections. Although CA methicillin-resistant *S aureus* (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.³⁻⁵

The molecular analysis of nosocomial and CA *S aureus* strains in the United States has shown that CA-MRSA isolates usually do not carry the *tst* gene, associated with toxic shock syndrome, but do harbor genes encoding other superantigen toxins capable of producing toxic shock-like illness.⁶ CA-MRSA organisms harboring the genes encoding Pantone-Valentine leukocidin (PVL) also have been associated with a severe course and poor prognosis in patients with pneumonia.^{7,8} Severe staphylococcal septicemia has been associated with serious underlying disease, intravenous drug abuse, or recent antibiotic or immunosuppressive therapy.⁹ Almost 30 years ago, Shulman and Ayoub described the rare occurrence of staphylococcal sepsis in the absence of predisposing factors in older children.¹⁰ Thus, the finding of several adolescents with severe infection caused by CA MRSA in a relatively short period of time prompted this review and a molecular characterization of the isolated strains.

METHODS

Since August 1, 2001, we have prospectively identified children with infections caused by CA *S aureus* at Texas Children's Hospital (TCH) in Houston, Texas. Staphylococci isolated from these

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patients are then recovered from the microbiology laboratory and sent to the Infectious Disease Research Laboratory, at which they are coded and frozen at -80°C in horse blood. Antibiotic susceptibilities (clindamycin, erythromycin, gentamicin, oxacillin, penicillin, trimethoprim-sulfamethoxazole, and vancomycin) are determined by disk-diffusion method and categorized according to National Committee for Clinical Laboratory Standards guidelines.¹¹ Clinical and demographic data for these patients are collected from the medical records and recorded by a research nurse using a standardized form (approved by the Baylor College of Medicine Institutional Review Board) and maintained in a computer database.

Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension.¹²⁻¹⁴ Patients who met criteria for severe sepsis and were admitted to the pediatric intensive care unit (PICU) were selected from the database. Charts were rereviewed for these patients and pediatric risk-of-mortality scores were obtained to assess predicted mortality rates.¹⁵ Patients >10 years old with sepsis were included in the study to best compare our findings with those of Shulman and Ayoub.¹⁰ Children with *S aureus* infections seen in consultation by the Infectious Disease Service at TCH were identified in the computer database of the service. Children with severe sepsis as defined above were determined by review of the electronic medical records.

Isolates recovered from these patients were grown on tryptic soy agar plates containing 5% sheep blood (BBL Beckton Dickinson, Cockeysville, MD) for DNA isolation. Template DNA from each strain was isolated by using the UltraClean microbial DNA kit as recommended by the manufacturer (Mo Bio Laboratories, Solano Beach, CA). Susceptibility to vancomycin was determined by microbroth dilution and categorized according to the 2004 National Committee for Clinical Laboratory Standards interpretative guidelines.¹⁶

Fingerprinting

All isolates were typed by repetitive-element polymerase chain reaction (REP-PCR) and pulse-field gel electrophoresis (PFGE). REP-PCR was performed by using a commercial REP-PCR fingerprinting kit according to manufacturer instructions (Bacterial Barcodes, Houston, TX). A PTC-200 Peltier thermocycler PCR system (MJ Research, Reno, NV) was used for the PCR, and the amplicons were separated by electrophoresis on a 1.5% agarose gel in $1\times$ TAE (0.04 M Tris-HCl/0.001 M EDTA).

PFGE was performed as follows: Agarose plug preparation and restriction enzyme digestion were performed by using the GenPath group 1 reagent kit (Bio-Rad Laboratories, Hercules, CA) according to manufacturer instructions. The plugs were digested with *Sma*I (GenPath kit) and loaded into the wells of a 1% agarose gel (Bio-Rad). Electrophoresis was performed in a CHEF-DR III (Bio-Rad) at 14°C by using the Harmony protocol parameters¹⁷: block 1 had an initial switch time of 5 seconds, a final switch time of 15 seconds, and a run time of 10 hours at 6 V/cm. Block 2 had an initial switch time of 15 seconds, a final switch time of 60 seconds, and a run time of 13 hours at 6 V/cm.

REP-PCR and PFGE fingerprints were visualized by UV light after ethidium-bromide staining and compared digitally by Pearson correlations/unweighted pair-group method with arithmetic mean using GelComparII computer software (Applied Maths, Kortrijk, Belgium). The relationship between strains was determined based on previously published criteria.¹⁸

Multilocus Sequence Type

Multilocus sequence typing was performed according to the instructions posted at the MLST Web site (www.mlst.net), and the sequence type (ST) was determined by using the *Staphylococcus* multilocus sequence type database located at Imperial College, London, and funded by the Wellcome Trust.

Determination of SCCmec Type

The SCCmec type was determined by using methods by Okuma et al.¹⁹ Positive controls were NCTC 10492, (SCCmec type I), N315 (SCCmec type II), 85/2082 (SCCmec type III), and CA 05 (SCCmec type IVa).

PCR Studies of Selected Genes

Primers for *cna*, PVL genes (*luk-S-PV* and *luk-F-PV*), and staphylococcal enterotoxin genes (*sea*, *seb*, *sec*, *sed*, *seh*, and *sej*) are

described elsewhere.^{20,21} Primers for *tst* (5'-gtaagcccttggcttgc-3' and 5'-tgtggatccgcattcattg-3') were designed by using a primer design program (Primer3, www.genome.wi.mit.edu/genome_software/other/primer3.html). Positive controls were UAMS-1 (*cna*), ATCC 51651 (*tst*), TCH clinical strain 584 (PVL genes), 85/2082 (*sea*), NCTC 10492 (*seb*), N315 (*sec*), clinical isolate 2949 (*sed* and *sej*), and MW2 (*seh*). The accuracy of the enterotoxin and *tst* PCR assays was confirmed by sequencing PCR products from the positive controls and performing BLAST analysis (www.ncbi.nlm.nih.gov/BLAST). The *cna* and PVL gene assays were confirmed previously.²¹

Case Reports

Case 1

A 14-year-old black male was admitted to TCH on September 13, 2002, with respiratory distress, rash, and swelling of his right knee. He had no significant past medical history and was in his usual state of health until September 6, 2002, when he sustained a right knee injury while playing football. At another hospital, an MRI was performed to evaluate the knee injury. Findings were consistent with a right knee effusion, and he was started on nonsteroidal antiinflammatory drugs. The swelling of the right knee continued to progress, and on September 11, he developed a pustular rash on his face and trunk, which was described as "varicella-like," and he began complaining of shortness of breath. He presented to the emergency center in obvious respiratory distress. He was awake and alert, breathing at a rate of 64 breaths per minute. His physical examination was remarkable for crackles in the lung fields bilaterally, pustular lesions on face and abdomen (Fig 1), and a swollen, tender right knee. He was leukopenic (total white blood cell count: $4700/\text{mm}^3$; neutrophils: 24%; band forms: 54%; lymphocytes: 9%) on admission, and his coagulation profile was abnormal (international normalized ratio: 1.9; D dimers: positive; fibrin split products: positive). He was intubated in the emergency center, and purulent secretions were obtained from the endotracheal tube. A chest radiograph showed bilateral nodules consistent with septic emboli. The patient required inotropic support and mechanical ventilation. Vancomycin, nafcillin, and gentamicin were initiated, and he was transferred to the PICU. Blood cultures from admission grew MRSA. Other cultures (tracheal secretions, synovial fluid of right knee, pustular lesions on skin) also grew MRSA. A transthoracic echocardiogram did not show vegetations. He was started on high-frequency oscillator ventilation because of persistent hypoxemia. On September 18, he developed increased intracranial pressure, with unequal pupils. A cerebral perfusion scan on September 19 showed absent cerebral blood flow and he was pronounced dead. He remained bacteremic throughout his hospital course. Autopsy results were not available.

Case 2

A 13-year-old white male with no significant past medical history was admitted to TCH from another hospital on July 28,

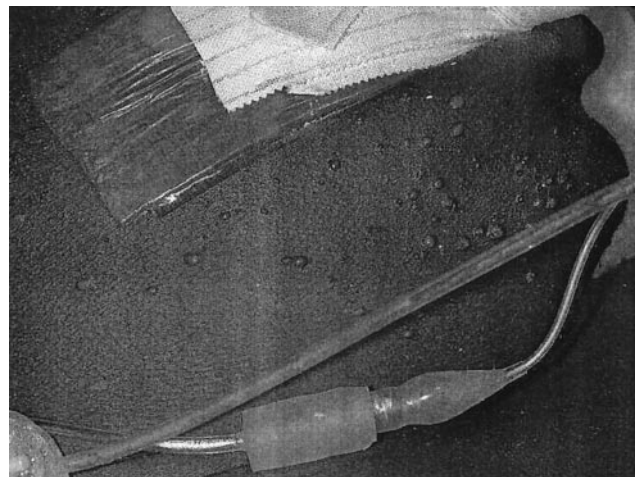


Fig 1. Pustular lesions in a patient with severe CA *S aureus* infection.

2003. Seven days before admission, he had stumbled on carpet and sustained mild trauma to his left lower extremity. Two days later, he began experiencing pain and swelling of his left knee and difficulty ambulating. An orthopedic specialist saw him as an outpatient and recommended a bone scan and an MRI. He was prescribed nonsteroidal antiinflammatory drugs. The swelling and pain of left knee intensified. The day before admission he developed generalized myalgias, cold sweats, difficulty breathing, and a rash over his lower extremities. He presented to the emergency center of another hospital on July 27. On physical examination, he was cold and clammy, diaphoretic, and toxic-appearing. His blood pressure was 86/47 mm Hg, and he was breathing at a rate of 66 breaths per minute. Pulmonary examination was remarkable for crackles bilaterally. His left knee was warm, tender, and swollen and had multiple vesicular-pustular lesions over both legs. He required endotracheal intubation, fluid boluses, and vasopressors. Blood cultures were drawn, and vancomycin and cefotaxime were initiated. The patient was transferred to the TCH PICU on July 28. Initial laboratory findings revealed a total white blood cell count of 15 000/mm³ (neutrophils: 22%; band forms: 68%; lymphocytes: 4%) and positive D dimers and fibrin split products, and chest radiographs were consistent with septic emboli. His antimicrobial regimen was changed to vancomycin, nafcillin, and gentamicin. An arthrocentesis of the left knee revealed 40 mL of purulent fluid. Gram-positive cocci in clusters visualized on the Gram-stain were subsequently identified as methicillin-susceptible *S aureus* (MSSA). Blood cultures from July 27 and 28 also yielded MSSA, as did cultured material from skin lesions. The patient developed multiple arrhythmias including ventricular tachycardia and asystole. A transthoracic echocardiogram did not show vegetations. He required cardiopulmonary resuscitation on several occasions. Because of his worsening cardiopulmonary condition and inability to maintain adequate oxygenation, extracorporeal membrane oxygenation was initiated. Despite all measures his condition continued to deteriorate, and he was pronounced dead on July 29, 2003. Autopsy results showed microabscesses in his lung, heart, laryngeal tissue, adrenal glands, and colon. There was inflammation of the conduction system, which probably explains the arrhythmias.

RESULTS

Between September 2002 and January 2004, 16 children met the definition of severe staphylococcal sepsis. Two children were <5 years old and were therefore excluded from the study. The average pediatric risk-of-mortality score for the 14 patients included in the study was 21 (the range is from 1 to 34, with normal being a score of zero), which translates into an average predicted mortality rate of 40.8%. Twelve patients (86%) had sepsis caused by MRSA, and 2 grew MSSA (Table 1). In the 3 years before the study (1999 to August 2001), only 1 patient (11 years old) was admitted to the PICU with sepsis caused by CA MRSA, and 2 (both 9 years old) were admitted for sepsis caused by CA-MSSA isolates. No deaths associated with *S aureus* sepsis were encountered in the prior 3 years.

Demographics and Epidemiology

The average age of the 14 patients was 12.9 years (range: 10–15 years). All were previously healthy with a mean weight of 63.0 kg and height of 1.67 m. Only 2 patients were female. Twelve patients (86%) had no underlying medical condition, 1 had mild intermittent asthma, and 1 had history of patent ductus arteriosus with a coil placed >1 year before the present disease onset. None of these patients had a history of recurrent abscesses. Eight children (57%) had experienced some sort of blunt trauma (ie, fall from bed, stumbled on a carpet), which in some instances heralded the initial site of presentation. The

TABLE 1. Severe CA *S aureus* Infections in Adolescents: Demographic and Clinical Data

Case	Age, y (12.9)*	Gender†	Race‡	Weight, kg (63.0)	No. of Bones and Joints Affected	Pulmonary Manifestations	Days of Bacteremia (4.3 d)	ICU Days (29.8)	Outcome
1	10	M	B	34.0	9	Bilateral air-space disease	11	53	Survived
2	13	M	B	40.0	6	Bilateral air-space disease and pneumatoceles	6	27	Survived
3	14	F	W	90.0	4	Septic emboli	7	42	Survived
4	14	M	B	94.5	1	Septic emboli	7	7	Died
5	12	M	W	70.8	8	Bilateral air-space disease and pneumatoceles	6	50	Survived
6	13	F	W	52.0	1	Septic emboli	1	2	Died
7	10	M	B	42.2	6	Empyema	7	44	Survived
8	12	M	B	55.0	10	Empyema and septic emboli	5	25	Survived
9	15	M	H	66.0	0	Bilateral air-space disease and pneumatoceles	0	120	Survived
10	13	M	W	55.0	3	Left lower lobe pneumonia and effusion	4	5	Survived
11	12	M	B	48.6	2	Bilateral air-space disease and septic emboli	1	22	Survived
12	15	M	H	55.0	1	Septic emboli	2	2	Died
13	14	M	W	104.0	2	None	1	1	Survived
14	14	M	W	76.0	2	Septic emboli	3	18	Survived

* Data in parentheses are means unless otherwise specified.

† M indicates male; F, female.

‡ B indicates black; W, white; H, Hispanic.

average time between the trauma and the presentation was 7 days. The average duration of symptoms before admission was 3.5 days (range: 2–7 days).

Three of the cases occurred in the month of October 2003, coinciding with the peak of the 2003 influenza virus season in Houston.

Clinical Manifestations

Bone and Joint Infections

Of the 14 children, 13 (93%) had bone and joint infections. Three children had septic arthritis of the knee joint, and the remaining 10 (71%) had multiple bones and joints involved with >2 sites affected simultaneously (range: 2–10). Of the 10 patients with >2 bones and joints affected, 8 also had pyomyositis of the neighboring muscles. *S aureus* was isolated from ≥ 1 bone/joint aspirates in 12 of the 13 patients.

Pulmonary

Of the fourteen patients, 13 (93%) had pulmonary involvement. Seven (50%) had bilateral nodular densities consistent with septic emboli seen on chest radiographs; these patients also had bone and joint infection. Three patients had bilateral air-space disease with multiple pneumatoceles, and 2 had complicated parapneumonic effusions. Eleven (79%) required endotracheal intubation secondary to respiratory failure. Nine of these patients (64%) grew *S aureus* from tracheal aspirates. Only 1 patient was admitted with primary pulmonary disease and was also coinfecting with influenza A virus.

Cardiovascular

All patients had a transthoracic echocardiogram, and none demonstrated vegetations. Only 1 patient had a transesophageal echocardiogram performed, which was also negative. Only 1 patient had left ventricular dysfunction on echocardiogram. The autopsy of 2 patients showed bacterial infiltrates in myocardium and endocardium, but no vegetations were seen on the valves.

Peripheral Vascular Disease

Four patients had vascular complications (29%). The common iliac vein was thrombosed in 1 patient, 2 had saphenous and popliteal vein thrombosis, and 1 had femoral vein thrombosis. All 4 patients had bone infections adjacent to their thromboses. Two of these patients had chest radiographs consistent with septic emboli. None of the patients had a family history of thrombosis, and subsequent evaluations for hypercoagulable state are still in progress. These thromboses developed early in the course of the infection and therefore did not seem to be related to prolonged immobilization. Two patients had low levels of protein C on presentation that later increased to normal levels.

Renal

Seven patients were admitted in acute pre-renal failure, and 1 patient had nephrotic syndrome on admission.

Skin

Eleven patients presented with skin lesions that ranged from hives to erythema multiforme-like rash to papular-pustular lesions (Fig 1). The content of these pustules was cultured and grew *S aureus*.

Clinical Course and Outcome

Of the 14 patients, 13 (93%) were bacteremic. The average duration of positive blood cultures was 4 days (range: 1–11 days). Eight (57%) patients were bacteremic for ≥ 4 days. These patients also had >2 bone/joint sites affected and had pulmonary lesions. The mean duration of fever was 13 days (range: 2–35 days), and the mean PICU stay was 30 days. Eight patients required surgical drainage of joints or incision and drainage of bone abscesses.

Three of the 14 patients died. MRSA was isolated from 2 of these patients and MSSA from 1. These 3 patients had septic arthritis of the knee without any other joints involved and pulmonary metastatic disease.

Patients were treated for the primary disease, which in the majority of cases was osteomyelitis. Only patients with vascular complications were treated as endovascular infections and received vancomycin for the complete 6 weeks of therapy; in addition, prolonged oral clindamycin was administered to 3 of these 4 patients.

Laboratory

The initial white blood cell count ranged from 2700/mm³ to 40 000/mm³ (mean absolute neutrophil count: 9700/mm³; range: 550–37 430/mm³). Four patients were leukopenic on admission, and 2 of them died. All patients had elevated erythrocyte sedimentation rates (mean: 80.6 mm/hour) and C-reactive proteins (mean: 33.5 mg/dL). All patients had positive D dimers and fibrin split products. Mean platelet count was 174 000/mm³ (range: 72 000–469 000/mm³). Although not all patients had hypofibrinogenemia, the disseminated intravascular coagulation panels were interpreted as suggestive of disseminated intravascular coagulation by the pathology service. Aspartate aminotransferase and alanine aminotransferase were also found to be elevated in 9 patients; serum albumin levels were low as well (mean: 2.43 g/dL). Hyponatremia was a common feature (mean: 130 mmol/L), and creatinine was >1.5 mg/dL in 5 of the 14 patients.

Antibiotic Susceptibility

The MRSA isolates from these patients had a similar antibiotic susceptibility pattern: all were susceptible by disk diffusion to clindamycin, gentamicin, vancomycin, and trimethoprim-sulfamethoxazole. All the MRSA isolates were resistant to erythromycin, with no inducible resistance to clindamycin. Vancomycin minimal inhibitory concentrations were obtained by microbroth dilution and ranged from 0.5 to 1.0 μ g/ml. The 2 MSSA isolates were also susceptible to clindamycin and trimethoprim-sulfamethoxazole.

Molecular Analysis

Twelve isolates were methicillin resistant, and all carried the SCC_{mec} type IV. All MRSA isolates were *tst*- and *cna*-negative, results consistent with previous findings for the predominant CA-MRSA clone circulating in Houston.²¹ Genes encoding for PVL were present in all isolates including the MSSA strains. The enterotoxin PCR assays were negative for all strains except 1 MSSA isolate that carried the enterotoxins genes *sed* and *sej* (Table 2).

REP-PCR and PFGE were performed to determine genetic relatedness. All MRSA isolates had identical or closely related banding patterns by REP-PCR, corresponding to the major clone that circulates in Houston (Fig 2). The 2 MSSA isolates differed only by the absence of 1 band. PFGE banding patterns are shown in Fig 3. Of the 12 CA-MRSA isolates, 10 had identical banding patterns and 2 differed by 1 band. The CA-MSSA isolates differed from the CA MRSA by no more than 3 bands and between each other by 1 band. Two CA-MRSA isolates and both CA-MSSA isolates were multilocus sequence typed and classified as sequence type (ST)8.

DISCUSSION

Only a small proportion of local infections or bacteremias caused by *S aureus* progress to severe sepsis.⁹ Commonly, this is associated with certain risk factors such as immunosuppression and advanced age, among others. In 1976, Shulman and Ayoub¹⁰ described 9 adolescent patients seen over a 3-year period who presented with severe sepsis caused by MSSA. These patients were considered unusual because of the severity of their illness as well as the noticeable absence of underlying medical conditions. Thereafter, few reports of severe *S aureus* sepsis in the pediatric population are found in the literature²² until 1999, when 4 fatal *S aureus* infections were reported in the Minnesota-North Dakota area.⁵ In these cases, CA MRSA was isolated. Since this report, several studies have reported severe sepsis syndrome caused by CA MRSA or related CA MSSA in diverse areas of the United States.^{4,23}

In surveillance of *S aureus* infection at TCH since August 2001, 74% of CA *S aureus* isolates in children have been methicillin (oxacillin) resistant. Ninety-five percent of the MRSA isolates have been recovered from patients with skin and soft tissue infections and 5% in patients with invasive disease. However, before September 2002, severe life-threatening CA-MRSA infections had not been frequently seen in otherwise healthy children at TCH.

The resemblance of the 14 patients described in this report to those described by Shulman and Ayoub is striking. In both studies, multiple bone and

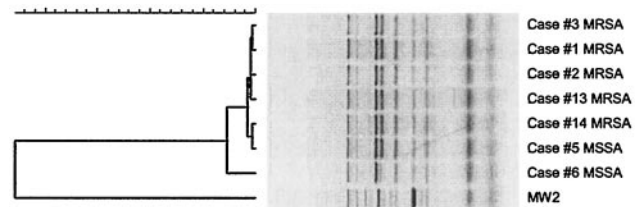


Fig 2. REP-PCR of 5 MRSA and 2 MSSA strains isolated from adolescent patients with severe CA *S aureus* sepsis and compared with MW2.

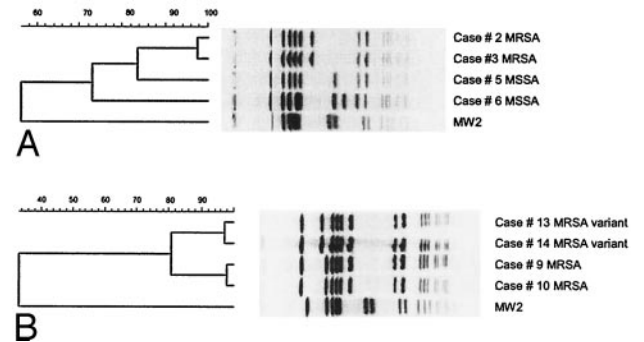


Fig 3. PFGE of strains isolated from adolescent patients with severe CA *S aureus* sepsis. a, The 2 MSSA isolates compared with 2 MRSA isolates and MW2. b, The MRSA isolates of the most common pattern and the variant compared with MW2.

joint infections as well as metastatic pulmonary disease are noticeable. Only 1 of our patients presented with a necrotizing pneumonia similar to that described in the patients in Minnesota, and this patient was coinfecting with influenza A virus. None of our patients fulfilled criteria for toxic shock syndrome.²⁴

Two younger children without underlying medical conditions (18 months and 4 years old) were also admitted to the PICU with severe CA-MRSA infections over the time period studied. In these 2 children, the sites of infection were lungs (pneumonia) and femur (osteomyelitis), respectively. Their isolates were identical to the predominant clone described in the adolescent patients. The 18-month-old patient admitted with pneumonia was coinfecting with influenza A and died shortly after admission. Autopsy findings were consistent with necrotizing pneumonia.

It is not clear what factors have played a role in the emergence of these severe cases seen at TCH. Shulman and Ayoub hypothesized in their study that a restriction in hexachlorophene use could have been a contributing factor through a potential increase in colonization of patients with *S aureus*. In another study from Africa²² in which 27 children with severe staphylococcal infections with no clear predisposing

TABLE 2. Characteristics of *S aureus* Strains Isolated From 14 Adolescent Patients With Severe Sepsis

Clinical Isolates	luk-S-PV ⁺	luk-F-PV ⁺	<i>tst</i>	<i>cna</i>	<i>sea</i>	<i>seb</i>	<i>sec</i>	<i>sed</i>	<i>seh</i>	<i>sej</i>	SCC _{mec}	MLST
MRSA (n = 12)	12/12		0/12	0/12	0/12	0/12	0/12	0/12	0/12	0/12	IV	ST8*
MSSA (n = 2)	2/2		0/2	0/2	0/2	0/2	0/2	1/2†	0/2	1/2†	NA	ST8*

NA indicates not applicable.

* Two MRSA and 2 MSSA were analyzed.

† Same isolate positive for *sed* and *sej*.

factors are described, poor environmental and personal hygiene was presumed to be an associated factor.

The deaths in children without typical risk factors in Minnesota-North Dakota in 1999 raised the concern of a highly virulent MRSA clone that had established itself in the community.^{23,25-27} The MW2 strain was isolated from 1 of these patients and subsequently sequenced completely.²⁸ This strain carried several virulence genes not present in other *S aureus* strains and was genetically defined as ST1 by multilocus sequence typing. In 2000, Mongkolrattanothai et al⁴ also isolated strains from 4 pediatric patients in Chicago, Illinois, who presented with severe sepsis syndrome. These strains were closely related to MW2. Two of the isolates were CA MSSA, which were indistinguishable from each other by PFGE and differed from the MRSA isolates by 2 bands (shown to contain the SCC*mec* type IV cassette).

Since 2002 a predominant clone, ST8, has been circulating in Houston.²¹ This clone is characterized by the presence of genes encoding for PVL, causes predominantly skin and soft tissue infections, and is most likely identical to the CA-MRSA strain USA300, which is present in various geographical regions of the United States.²⁹⁻³¹

Two other clones circulate in Houston at a much lower level (ST30 and ST1). We had hypothesized that the less common ST1, likely related to the MW2 strain (which caused the pediatric deaths in Minnesota and severe disease in Chicago), also would be associated with the severe cases observed at our hospital. On the contrary, we found that all staphylococcal isolates recovered from these patients were closely related to (MSSA isolates) or indistinguishable from (MRSA isolates) the predominant CA-MRSA clone in Houston (ST8).

This clone is responsible for causing a wide spectrum of diseases ranging from simple soft tissue infections to severe cases such as those described in this report. In accordance with the observations by Mongkolrattanothai et al,⁴ the MSSA and MRSA isolates in our study were closely related, suggesting the possible derivation of CA MRSA from a CA MSSA by acquisition of the SCC*mec* type IV cassette and horizontal transfer in the community.²¹

Secondary bacterial infections, especially with *S aureus*, are not uncommon in epidemics of influenza. The association between influenza virus and staphylococcal pneumonia has been established, and the clinical presentation includes a characteristic necrotizing pneumonia.¹ Gillet et al⁸ described patients (median age: 14.8 years) with CA *S aureus* necrotizing pneumonias who had complaints of flu-like symptoms several days before their hospital admission. Whether initial viral infections lead to changes in the respiratory mucosa that resulted in enhanced bacterial adhesion was unclear. The majority of these patients were infected with strains carrying the PVL genes (*luk-S-PV* and *luk-F-PV*), rarely carried by European strains. In Houston, virtually all CA-MRSA strains carry the PVL genes, and the association between these genes and severe cases is less obvious.

However, Martinez-Aguilar et al³² recently reported that more severe complications such as deep venous thrombosis are seen in patients with musculoskeletal infections caused by CA *S aureus* isolates carrying the PVL genes than in patients with these infections caused by *S aureus* isolates lacking the PVL genes. In addition to PVL genes, the staphylococcal enterotoxin genes have been implicated as important virulence determinants in the multifactorial pathogenicity of *S aureus*. In the 4 cases from Chicago,⁴ all strains carried PVL genes, *sea* and *seh*. The MRSA isolates carried *sec*, and MSSA isolates carried *seb*. In our 14 patients, only 1 MSSA strain carried any of the enterotoxin genes (*sed* and *sej*) that were sought.

The 2003-2004 influenza season in Houston began earlier than in previous seasons, with a peak of cases occurring in October 2003. Three of the 14 children with severe sepsis were admitted in the month of October 2003. Ten of our patients had viral cultures performed, but only 1 had influenza A isolated. This patient presented with necrotizing pneumonia.

CONCLUSIONS

Previously healthy adolescents without predisposing risk factors have presented more frequently at our hospital with severe staphylococcal infections since September 2002. Primarily CA MRSA, but also clonally related CA MSSA (all closely related to the predominant TCH clone), has been isolated from these patients. Because this clone is also the predominant cause of skin and soft tissue infections in our community, other factors such as host immunity, hormonal factors, and protein expression may be playing a role in the pathogenesis of these severe infections in adolescents. Finally, the clinician is again reminded that *S aureus*, especially CA MRSA, can cause severe life-threatening infections in otherwise healthy adolescents.

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Severe Staphylococcal Sepsis in Adolescents in the Era of Community-Acquired Methicillin-Resistant *Staphylococcus aureus*

Blanca E. Gonzalez, Gerardo Martinez-Aguilar, Kristina G. Hulten, Wendy A. Hammerman, Jorge Coss-Bu, Anna Avalos-Mishaan, Edward O. Mason, Jr and Sheldon L. Kaplan

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