

## BRIEF REPORT

## *Staphylococcus aureus* Sepsis and the Waterhouse–Friderichsen Syndrome in Children

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## SUMMARY

*Staphylococcus aureus* has increasingly been recognized as a cause of severe invasive illness. We describe three children who died at our institution after rapidly progressive clinical deterioration from this infection, with necrotizing pneumonia and multiple-organ-system involvement. The identification of bilateral adrenal hemorrhage at autopsy was characteristic of the Waterhouse–Friderichsen syndrome, a constellation of findings usually associated with fulminant meningococemia. The close genetic relationship among the three responsible isolates of *S. aureus*, one susceptible to methicillin and two resistant to methicillin, underscores the close relationship between virulent methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus* isolates now circulating in the community.

**S**TAPHYLOCOCCUS AUREUS IS A UBIQUITOUS BACTERIUM THAT CAUSES infection in all age groups. The increasing recognition of isolates circulating in the community that are resistant to methicillin has increased the level of concern about this important pathogen and perhaps has led to the identification of several “new” clinical syndromes.

Mongkolrattanothai et al. recently described four patients with a clinical syndrome called severe sepsis.<sup>1</sup> We have defined this term, originally used by Shulman and Ayoub,<sup>2</sup> as isolation of *S. aureus* from a clinically important site, hypotension (systolic blood pressure below the 5th percentile for age for children or less than 90 mm Hg for adults), respiratory distress syndrome or respiratory failure, plus involvement of the central nervous system, liver, kidneys, muscles, or skin or hemostasis (or a combination) or the presence of leukopenia or thrombocytopenia. The syndrome is similar to the toxic shock syndrome but does not fulfill all the clinical criteria for that syndrome as defined by the Centers for Disease Control and Prevention (CDC).<sup>3</sup>

Two of the patients described by Mongkolrattanothai et al. had infections caused by methicillin-susceptible *S. aureus* (MSSA) isolates, and two had infections caused by methicillin-resistant *S. aureus* (MRSA) isolates; one died. Pulsed-field gel electrophoresis (PFGE) of the MSSA and MRSA isolates from all the patients revealed identical patterns except for the difference associated with the insertion of SCC<sub>mec</sub>, an integrated genomic island harboring the *mecA* gene that confers methicillin resistance.<sup>1</sup> The MRSA isolates were identical to MW2, an isolate of community-associated MRSA whose genome was sequenced<sup>4</sup> with both PFGE and multilocus sequence typing. MW2 and three clonally identical MRSA isolates were responsible for fatal, severe sepsis caused by community-

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associated MRSA in children in Minnesota and North Dakota<sup>5</sup> and had previously been implicated in community-associated MRSA infections in children in Chicago.<sup>6</sup>

We have subsequently cared for two additional children with severe sepsis syndrome; both died. All three patients underwent postmortem evaluation. This report presents the pathologic features of these three fatal cases.

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#### CASE REPORTS

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All three patients had clinical findings of the Waterhouse–Friderichsen syndrome, characterized by petechial rash, coagulopathy, and cardiovascular collapse (Table 1). The etiology of *S. aureus* in two of the patients was established with antemortem respiratory cultures and the findings at postmortem examination; the third patient had bacteremia. Two of the patients were receiving extracorporeal membrane oxygenation immediately before death. All three patients had generally been in good health before the onset of severe sepsis caused by *S. aureus*, and all had been given vancomycin and ceftriaxone in the emergency department. All three had rapidly progressive clinical deterioration with leukopenia, neutropenia, severe metabolic acidosis, profound tachycardia, and secondary hypotension during their brief clinical illnesses. At admission, all three patients had a normal or slightly acidemic blood pH (7.40, 7.42, and 7.29, respectively), which worsened rapidly despite aggressive supportive care and measured 7.11, 6.96, and 7.01 after four, eight, and four hours, respectively.

The clinical features of Patient 1 have been described previously.<sup>1</sup> This 15-month-old girl presented with upper and lower respiratory tract symptoms of four days' duration. On evaluation, she had severe pneumonia with pleural effusion, hepatic dysfunction, thrombocytopenia, and coagulopathy. She died eight hours after arriving in the emergency department. Cultures of antemortem blood and pleural fluid yielded MSSA.

Patient 2 was a nine-month-old female who presented with fever and respiratory symptoms of two days' duration. In the emergency department, she was febrile and had tachycardia and tachypnea. Chest radiography revealed extensive infiltrates in the right middle and lower lobes. In the intensive care unit, she was intubated, but ST-segment elevation and asystole developed, from which she was resuscitated. On her second day in the hospital, wors-

ening cardiac and pulmonary function prompted implementation of extracorporeal membrane oxygenation. The girl had cool extremities, and a diffuse, patchy, dark rash had developed. Her condition continued to deteriorate, with progressive multiorgan-system failure. Bradycardia developed, and she died. An antemortem culture from her endotracheal tube grew MRSA.

Patient 3 was a 17-month-old male with a history of reactive airway disease and pharyngitis treated with amoxicillin–clavulanate and oral corticosteroids for two weeks before admission. He was evaluated in the emergency department for respiratory distress and an episode of nonbilious, nonbloody vomiting. A radiograph of the chest revealed patchy atelectasis interpreted to be consistent with sequelae of asthma. A viral syndrome was presumed, and the patient was discharged. Four hours later he returned in severe respiratory distress. He was lethargic but rousable, although he rapidly became obtunded and intubation was performed. Cardiac and respiratory function continued to deteriorate. He was placed on extracorporeal membrane oxygenation. Petechiae, purpura, and signs of multiorgan-system failure progressed despite support with extracorporeal membrane oxygenation. This support was withdrawn, and the boy died. An antemortem culture from his endotracheal tube grew MRSA.

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#### MICROBIOLOGIC METHODS

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*S. aureus* isolates were identified by typical colony morphology, typical Gram's stain appearance, and positive results with the Staphaurex test (Murex Biotech).

To prepare for pulsed field gel electrophoresis (PFGE), whole-cell DNA was prepared and digested in agarose plugs with *Sma*I as described previously.<sup>7,8</sup> Restriction fragments were resolved with an electrophoresis apparatus (CHEF DR III, Bio-Rad Laboratories) with the following settings: 6 V per centimeter, 14°C, initial time of 5 seconds, final time of 40 seconds, during a period of 20 hours. The relatedness of strains was determined by comparing their restriction-fragment-length polymorphisms according to the guidelines of Tenover et al.<sup>9</sup>

Multilocus sequence typing was performed as described previously.<sup>1,10</sup> The allelic profile of *S. aureus* isolates was obtained by sequencing internal fragments of seven “housekeeping” genes and submitting them to the Multi Locus Sequence Typing

**Table 1. Characteristics of Three Children with Fatal, Severe Sepsis Caused by *S. aureus*.**

Characteristic	Patient 1*	Patient 2	Patient 3
Date of admission	July 2000	April 2003	April 2004
Interval between hospitalization and death	8 hr	6 days	1 day
Age	15 mo	9 mo	17 mo
Sex	Female	Female	Male
Clinical features			
Hypotension	Yes	Yes	Yes
Tachycardia (beats/min)	212	225	190
Pneumonia	Yes	Yes	Yes
Pleural effusion or empyema	Empyema	Empyema	Pleural effusion
Ascites	No	No	Yes
Rash	Petechial	Diffuse, patchy, purpuric	Petechial and desquamating
Microbiologic features			
<i>S. aureus</i> bacteremia	Yes	No	No
Other antemortem isolation of <i>S. aureus</i>	Pleural fluid	Tracheal aspirate	Tracheal aspirate
Laboratory data†			
Creatinine (mg/dl)	1.0	1.7	1.2
Urinalysis	Proteinuria, hematuria	Proteinuria, hematuria	Proteinuria, trace of hematuria
Serum creatine kinase (U/liter)	ND	4932	84
Serum aspartate aminotransferase (U/liter)	122	172	88
Serum alanine aminotransferase (U/liter)	16	57	11
Initial cortisol (μg/dl)	74	67	ND
Coagulopathy			
Prothrombin time (sec)	38.0	32.7	29.6
Activated thromboplastin time (sec)	>100	56.4	141.4
White-cell count (per mm <sup>3</sup> )	4,600	1,300	1,000
Absolute neutrophil count (per mm <sup>3</sup> )	1,100	50	200
Platelet count (per mm <sup>3</sup> )‡	37,000	37,000	81,000
Blood gas data§			
pH	7.40 to 7.11	7.42 to 6.96	7.29 to 7.01
PCO <sub>2</sub> (mm Hg)	29 to 40	26 to 73	41 to 67
PO <sub>2</sub> (mm Hg)	108 to 62	225 to 34	31 to 57
HCO <sub>3</sub> <sup>-</sup> (mmol/liter)	17 to 13	16 to 15	19 to 16
Base excess	-6 to -15	-6 to -16	-6 to -14

\* The clinical features of Patient 1 were reported previously.<sup>1</sup>

† In patients for whom more than one abnormal value was obtained, the greatest deviation from normal is shown. ND denotes not done.

‡ These numbers indicate the presence of thrombocytopenia in all three patients.

§ Blood gas data show the interval from the time of admission until four, eight, and four hours after admission for Patients 1, 2, and 3, respectively. The data for Patient 3 are from a venous source. PCO<sub>2</sub> denotes the partial pressure of carbon dioxide (normal range, 35 to 45 mm Hg), PO<sub>2</sub> the partial pressure of oxygen (normal range, 75 to 100 mm Hg), and HCO<sub>3</sub><sup>-</sup> bicarbonate. The fraction of inspired oxygen varied among the patients but was always greater than 0.21.

home page (www.mlst.net), where seven numbers depicting the allelic profile were assigned to the isolate and defined its type. Screening of isolates for the Pantón–Valentine leukocidin (PVL) genetic determinants was performed with the use of polymerase-chain-reaction amplification with the primer pair PVL1 and PVL2 (final concentration, 10  $\mu$ M), which produces a 3.5-kb product<sup>1</sup> encompassing the entire *lukF-PV* and *lukS-PV* open reading frames and surrounding DNA. SCC *mec* typing was performed as described.<sup>1</sup>

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## RESULTS

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### MICROBIOLOGIC FINDINGS

The MSSA and MRSA isolates from all three patients were clonal according to PFGE and multilocus sequence typing (data not shown) except for a two-fragment difference that was previously shown<sup>1</sup> to reflect the insertion of SCC*mec* type IV into the MRSA isolates. All three isolates were multilocus sequence type 1 and harbored the Pantón–Valentine leukocidin determinants.

### PATHOLOGICAL FINDINGS

Postmortem examination revealed necrotizing bronchopneumonia and bilateral adrenal hemorrhage in all three patients. All patients had similar gross findings at autopsy. Involvement of the skin ranged from petechiae to desquamating, dusky rashes. Gross and histologic findings of bilateral necrotizing bronchopneumonia, pulmonary edema, and adrenal hemorrhage were present in all patients (Fig. 1). In all patients the lungs had many demonstrable gram-positive cocci in clusters occasionally found in the walls of pulmonary vasculature. The severity of adrenal hemorrhage ranged from about 30 percent to complete hemorrhagic infarction. Pathological findings indicative of overwhelming sepsis and disseminated intravascular coagulation were also noted. None of the patients had any gross or microscopical anatomic evidence of endocarditis or myocarditis. Patient 1 had anasarca, mild-to-moderate cerebral edema, splenic and hepatic congestion, and petechial hemorrhages on the surfaces of the heart, lungs, kidneys, and intestinal serosa. Patient 2 had epicardial hemorrhages, acute tubular necrosis, and macrovesicular steatosis; brain dissection was not performed. Patient 3 had anasarca, petechial hemorrhages on the liver surface, glomerular fibrin microthrombi, and mild cerebral edema.

### REVIEW OF PATIENTS WHO RECEIVED EXTRACORPOREAL MEMBRANE OXYGENATION

A search of the University of Chicago archives of pediatric and neonatal autopsies from 1992 to November 2004 was performed with the search parameters of extracorporeal membrane oxygenation and adrenal hemorrhage. Twenty-one pediatric and neonatal patients were receiving extracorporeal membrane oxygenation at death, and three met the search criteria. A review of the results of these three autopsies revealed no adrenal hemorrhage in one patient, focal hemorrhage in multiple organs in the second, and severe, generalized hemorrhage in the third. Thus, fatal illnesses in patients receiving extracorporeal membrane oxygenation were not associated with bilateral adrenal hemorrhage.

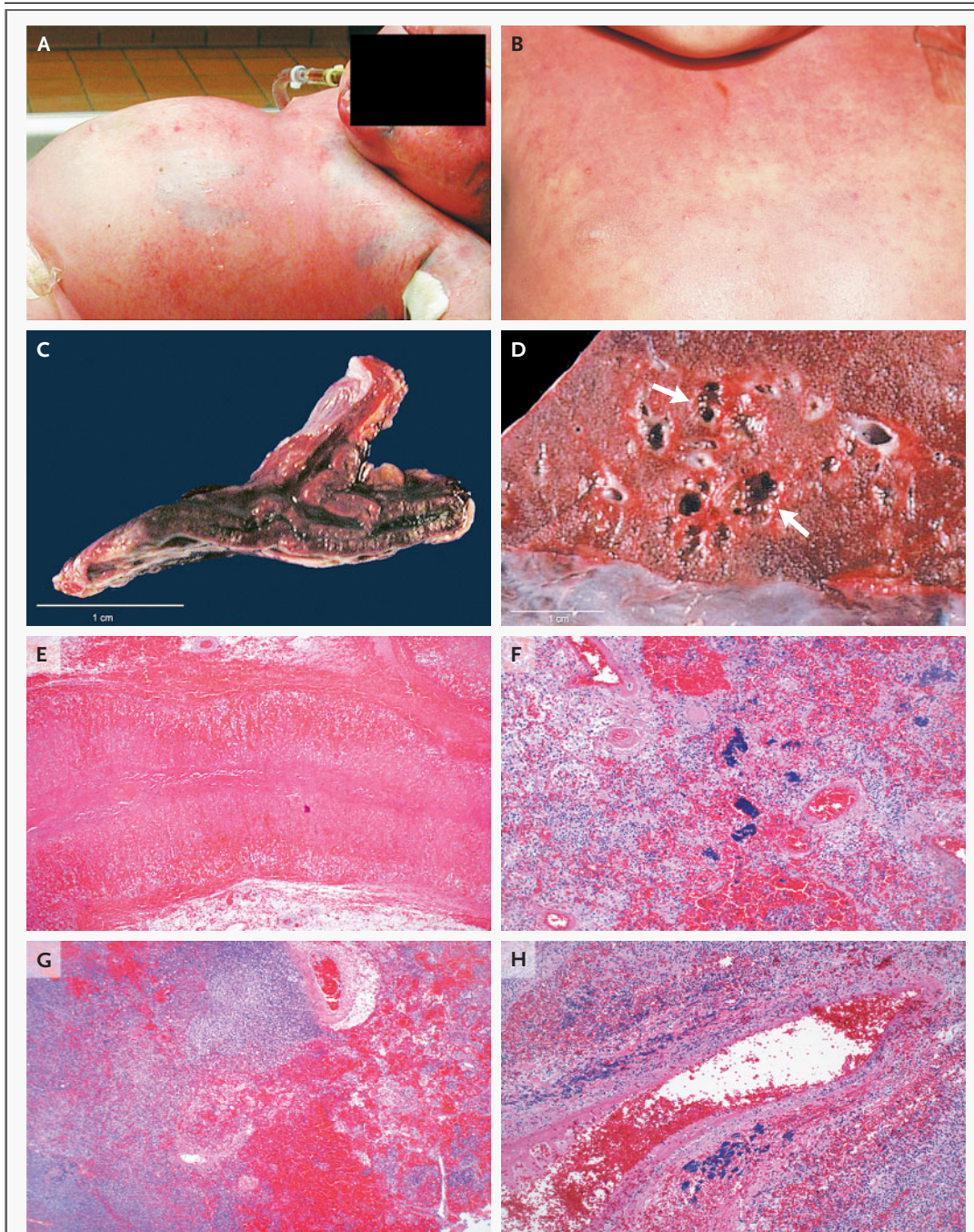
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## DISCUSSION

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The Waterhouse–Friderichsen syndrome, first reported in 1911 by Rupert Waterhouse, is characterized by petechial rash, coagulopathy, cardiovascular collapse, and bilateral adrenal hemorrhage.<sup>11</sup> The syndrome is generally associated with fulminant meningococemia; cases of purpura fulminans, cutaneous ecchymosis, hypotension, and fever<sup>12</sup> in patients for whom the culture data are unknown or unavailable have been classified as probable meningococemia by the CDC.<sup>13</sup>

Other organisms may occasionally be associated with this syndrome. Carl Friderichsen found that about 20 percent of 250 cases were caused by other organisms, usually *Streptococcus pneumoniae*.<sup>14</sup> A recent report of nonmeningococcal Waterhouse–Friderichsen syndrome cited two cases of *S. pneumoniae* and one case caused by beta-hemolytic streptococcus.<sup>15</sup> Reportedly, organisms such as *Neisseria gonorrhoeae*, *Escherichia coli*, and *Haemophilus influenzae* type b have also occasionally caused the Waterhouse–Friderichsen syndrome.<sup>16–18</sup> However, *S. aureus* has not been well documented as a cause of the Waterhouse–Friderichsen syndrome, although this species has increasingly been identified as a cause of severe sepsis, necrotizing bronchopneumonia, and death.<sup>1</sup> In one of his original descriptions, Friderichsen cited *Staphylococcus albus* as an etiologic agent, although that coagulase-negative species was probably a contaminant.<sup>19</sup> In a review published in 1955, Friderichsen mentioned a child who died with “adrenal apoplexy” found at autopsy and with *S. aureus* “demonstrated.”<sup>14</sup> An adult in Poland had pulmonary, pleural, and microscopical adrenal



**Figure 1. Clinical and Pathological Findings in Three Patients with Fatal Cases of Sepsis Caused by *S. aureus*.**

Panel A shows the petechial and desquamating rash in Patient 3, and Panel B the petechial rash in Patient 1. Panel C shows a cross-section of an adrenal gland in Patient 3 with gross hemorrhage throughout. The lung of Patient 3 with microabscesses (arrows) is shown in Panel D. Panel E depicts the adrenal gland with diffuse hemorrhagic infarction, Panel F a lung with bacterial colonies and hemorrhage, Panel G a lung with complete destruction of the alveolar architecture and extensive polymorphonuclear infiltrates, and Panel H septic vasculitis with prominent bacterial colonies in a vessel wall (hematoxylin and eosin). These clinical and pathological findings were demonstrable in all three patients.

hemorrhage documented post mortem; a staphylococcal infection was said to be the cause, but the species was not reported.<sup>20</sup>

Our patients clearly show that *S. aureus* should now be added to the list of etiologic agents of the Waterhouse–Friderichsen syndrome. Also, some patients currently included in surveillance of meningococcal disease may have severe sepsis caused by *S. aureus*.

Some clinical features of our patients have been noted by others during invasive *S. aureus* infections. For example, *S. aureus* caused 7 of 143 cases of septic shock at the Arkansas Children’s Hospital.<sup>21</sup> Petechial skin lesions have been noted in “septicemia” caused by *S. aureus*, especially with associated endocarditis. Purpura has also been described.<sup>22,23</sup>

The cases of sepsis in our patients cannot be explained by hemorrhage related to extracorporeal membrane oxygenation. The review of postmortem data from our institution suggested that anticoagulation associated with extracorporeal membrane oxygenation does not cause bilateral hemorrhage limited to the adrenal glands, although unilateral hemorrhage into an adrenal gland has been documented in a small number of patients receiving extracorporeal membrane oxygenation.<sup>24</sup> Furthermore, bilateral hemorrhage limited to the adrenal glands occurred in all three of our patients, including Patient 1, who did not receive extracorporeal membrane oxygenation.

The isolates from two of our patients were resistant and the third was susceptible to methicillin. However, all isolates were clonally related and belonged to multilocus sequence type 1. According to the PFGE-based nomenclature of McDougal et al., these isolates can be classified as USA400.<sup>25</sup> The clonal relatedness of these MSSA and MRSA isolates is of interest.

MRSA isolates have emerged in the community in many parts of the world.<sup>26–28</sup> It is believed that many of these community-associated MRSA strains have arisen when a genomic island mediating methicillin resistance, called staphylococcal cassette chromosome *mec* type IV (SCC*mec* IV), was acquired by *S. aureus* with a methicillin-susceptible background.<sup>29,30</sup> After a report of fatal illness in four children with community-associated MRSA, one of the responsible isolates, MW2, was sequenced in its entirety.<sup>4</sup> Nineteen virulence genes including

11 exotoxins and 4 enterotoxins were found in the genomic sequence that were not present in other genomes of *S. aureus* that were sequenced.

MW2 seems to have evolved from MSSA 476, a clinical isolate also belonging to multilocus sequence type 1 that was responsible for osteomyelitis in an otherwise healthy nine-year-old boy.<sup>31</sup> MW2 seems to have acquired SCC*mec* IV, the *S. aureus* pathogenicity island SaPI3, and the bacteriophage  $\phi$ Sa2 in its evolution from MSSA 476. The latter two of these DNA inserts in the MW2 genome resulted in the acquisition of genes encoding three toxins including Pantón–Valentine leukocidin. Pantón–Valentine leukocidin is a two-component leukocyte toxin believed to be important in the pathophysiology of skin and soft-tissue infections and necrotizing pneumonia,<sup>32–34</sup> whose genetic determinants were found in all isolates from our patients. Which toxins, if any, in addition to Pantón–Valentine leukocidin are responsible for the clinical manifestations in our patients is unknown.

The clinical course of disease in these patients resembles that of fulminant meningococcemia and represents the severe extreme of invasive *S. aureus* disease. Clinical features of special note include leukopenia and neutropenia, profound tachycardia, and profound metabolic acidosis that worsened rapidly despite prompt institution of intensive care.

The recent increase in the clinical burden caused by *S. aureus* reflects epidemic community-associated MRSA in many locales where skin and soft-tissue infections have predominated. However, increasing numbers of reports of invasive disease such as necrotizing pneumonia,<sup>1,28,34</sup> multifocal skeletal infections, and necrotizing fasciitis,<sup>35</sup> as well as severe sepsis, serve as a reminder that this species can cause severe illness and that its pathophysiology remains incompletely understood.

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