Waterhouse-Friderichsen Syndrome with Bilateral Adrenal Hemorrhage Associated with Methicillin-Resistant *Staphylococcus aureus* (MRSA) Bacteremia in an Adult Patient with History of Intravenous Drug Use

EF Thomas Kalinoski

Corresponding Author: Thomas Kalinoski, e-mail: kalli0136@umn.edu

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Patient: Male, 58-year-old

Final Diagnosis: MRSA infection • Waterhouse-Friderichsen syndrome

Symptoms: Shock • weakness

Medication: —

Clinical Procedure: —

Specialty: Critical Care Medicine • Endocrinology and Metabolic • Infectious Diseases

Objective: Unusual clinical course

Background: Waterhouse-Friderichsen syndrome, also known as acute adrenal insufficiency due to adrenal gland hemorrhage, is an uncommon and frequently fatal condition classically presenting with fever, shock, rash, and coagulopathy. Although most often associated with Meningococcemia, many other etiologies have been implicated, including reports of *Staphylococcus aureus* infection on autopsy examinations. This report details an adult intravenous drug user with adrenal hemorrhage associated with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia.

Case Report: A 58-year-old man with a history of intravenous drug use presented to the hospital with weakness. Vitals were initially normal and exam findings were notable for decreased right-sided motor strength. Magnetic resonance imaging (MRI) revealed a cervical epidural abscess with spinal cord compression. Despite initiation of broad-spectrum antibiotics and intravenous fluids, the patient progressed to shock, requiring vasopressor administration, and his blood cultures later grew MRSA. Further imaging of the abdomen/pelvis was completed, revealing bilateral adrenal hemorrhage. Random cortisol at that time was 5.6 µg/dL, confirming a diagnosis of critical illness-related corticosteroid insufficiency in addition to likely septic and spinal shock. The patient was initiated on hydrocortisone with improvement in his hypotension. He was transitioned to prednisone and fludrocortisone in addition to 8 weeks of antibiotics after achieving clinical stability.

Conclusions: This report brings to attention the risk of adrenal hemorrhage and acute adrenal insufficiency as a sequela of the relatively common illness of *Staphylococcus aureus* bacteremia. As symptoms of adrenal insufficiency can overlap with septic shock related to the primary condition, this diagnosis requires a high index of suspicion in the critically ill patient.

Keywords: Adrenal Insufficiency • Bacteremia • Waterhouse-Friderichsen Syndrome

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**Background**

Waterhouse-Friderichsen syndrome describes the phenomenon of acute adrenal insufficiency in the setting of bilateral adrenal hemorrhage, originally defined in the setting of *Neisseria meningitidis* bacterial sepsis in children [1]. The principal manifestation of this disorder is overt shock, although other signs and symptoms include petechial rash, coagulopathy, generalized weakness, fatigue, nausea/vomiting, and confusion [2]. Although occurring most commonly in children and over 80% of cases associated with *Neisseria meningitidis*, this condition has since been described in adults and other etiologies have been identified, including *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Capnocytophaga canimorsus*, *Proteus mirabilis*, and *Rickettsia rickettsii* among other bacterial, viral, and non-infectious etiologies [1-14].

Despite being one of the leading causes of bloodstream infections, the organism *Staphylococcus aureus* has been so far described as an etiologic agent for Waterhouse-Friderichsen syndrome in just a few published cases to the author’s best knowledge (Table 1). Of those found, 3 studies were postmortem autopsy cases of children and adults and 1 was a clinical case involving a child [13-16].

The first of these case series involved a postmortem examination of 800 cases of septic shock in children and adults. Ultimately, 5 of the specimens were found to reveal adrenal hemorrhage. Two of those 5 patients (1 child and 1 adult) had either pre- or postmortem cultures growing *Staphylococcus aureus*, 1 of which was MRSA [13].

Another case series that involved both children and adults who died of fatal bacterial infection, with 65 specimens sent to the Centers for Disease Control (CDC) found 4 cases of bilateral adrenal hemorrhage in patients with *Staphylococcus aureus* infection detected by immunohistochemical staining [14]. Due to the nature of the study, the resistance pattern of these organism was unknown and the exact numbers of children and adults was not specified.

An additional study described 3 children with *Staphylococcal aureus* infection at an academic hospital, all of whom died [15].

![Table 1. Comparison of clinical characteristics of published cases involving *Staphylococcus aureus*-associated adrenal hemorrhage.](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAIlAAAAHgCAYAAAAv9oivAAAABGUrFhPz9v/f39/f59/f79/f99/v19/v39/v59/v79/v99/v119/v139/v159/v179/v199/v219/v239/v259/v279/v299/v319/v339/v359/v379/v399/v419/v439/v459/v479/v499/v519/v539/v559/v579/v599/v619/v639/v659/v679/v699/v719/v739/v759/v779/v799/v819/v839/v859/v879/v899/v919/v939/v959/v979/v999/wAAAABnSUwBAMAAAAmJHRMnSITmYiCII4gAAAAAASUVORK5CYII=)

| Source   | Age | Sex | Outcome | Organism diagnosis           | Methicillin susceptibility | Adrenal hemorrhage diagnosis | Endocrine Testing | Source infection | Rash | Coagulopathy |
|----------|-----|-----|---------|--------------------------------|---------------------------|-----------------------------|------------------|----------------|------|-------------|
| Tormos [13] | 2 yrs | Male | Death   | Blood culture, postmortem     | Resistant                 | Autopsy                     | No               | Pneumonia       | -    | -           |
| Guarner [14] | 34 yrs | Male | Death   | Blood culture, premortem      | Susceptible               | Autopsy                     | No               | Myositis        | -    | -           |
| Adem [15] | 15 mos | Female | Death   | Blood culture, premortem      | Susceptible               | Autopsy                     | No               | Pneumonia       | Yes  | Yes         |
|          | 9 mos  | Female | Death   | Respiratory culture, premortem| Resistant                 | Autopsy                     | No               | Pneumonia       | Yes  | Yes         |
|          | 17 mos | Male  | Death   | Respiratory culture, premortem| Resistant                 | Autopsy                     | No               | Pneumonia       | Yes  | Yes         |
| Mukherjee [16] | 7 yrs | Male  | Death   | Blood culture, premortem      | Susceptible               | Adrenal ultrasound           | No               | Cellulitis       | Yes  | Yes         |

“-” indicates that parameter was not indicated in cited article.
Bilateral adrenal hemorrhage was discovered on autopsy in all cases. One of the patients had been diagnosed with *Staphylococcus aureus* bacteremia prior to death, while the organism was discovered by respiratory cultures for the other 2 cases. Two of the 3 cases were due to MRSA. It appears that none of these patients had diagnostic testing for adrenal insufficiency before or after death and none had received steroid medication.

The final publication is a case report of a 7-year-old boy with methicillin-resistant *Staphylococcus aureus* (MSSA) toxic shock syndrome and bacteremia [16]. Adrenal hemorrhage was suggested by adrenal ultrasound. Although cortisol levels were not assessed, the patient was started on empiric hydrocortisone but unfortunately died shortly afterwards.

The present report is of a 58-year-old man with a history of intravenous (i.v.) drug use with adrenal hemorrhage and Waterhouse-Friderichsen syndrome associated with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia.

### Case Report

A 58-year-old man with a history of alcohol and methamphetamine use disorders and hypertension was brought into the emergency room by ambulance with right-sided weakness resulting in a ground-level fall. The patient described weakness in the right upper and lower extremities, which had resulted in difficulty walking. The weakness resulted in him falling onto his back and hitting his head without losing consciousness. The patient denied numbness, bowel or bladder incontinence, or other neurological symptoms. He endorsed recent shortness of breath but no cough, fevers, or rash. A complete review of symptoms was otherwise normal. The patient did endorse i.v. drug use with methamphetamine and recently fentanyl. He was not taking any anticoagulant medications.

On presentation, the patient’s blood pressure was 111/62, pulse 102 beats/minute, respirations 20/minute, peripheral oxygen saturation (SpO2) 95% on room air, and temperature 38.4°C. The examination was remarkable for scattered bruising and track marks without a rash or frank purpura. No murmurs or cracks were appreciated. He was noted to have cervical spine tenderness to palpation. Strength in the right upper and lower extremities was 3/5, and strength elsewhere was 5/5. Reflexes were diminished globally. Gait testing was not possible due to the degree of weakness. The patient was alert but oriented to only self and place. The rest of the neurological exam, including cranial nerves, sensation, and cerebellar function, was normal. Initial laboratory studies were remarkable for a white blood count of 14 700/µL with 87% neutrophils. The platelets were 306 000/µL and hemoglobin was 12.4 g/dL. International normalized ratio (INR) was 1.3. Electrolytes, kidney and liver function tests, bilirubin, lactate, and creatine kinase were normal (Table 2). Blood cultures were drawn at that time.

Other pertinent diagnostic studies include a negative sputum culture, interferon gamma release assay (IGRA), human immune deficiency virus (HIV) serology, coronavirus disease 2019 (COVID-19) nucleic acid test, cryptococcal antigen, aspergillus serology and galactomannan antigen, histoplasmosis, blastomycosis, and coccidioides serology, 1,3-beta-d-glucan, and legionella urine antigen. Thyroid-stimulating hormone (TSH), antineutrophil cytoplasmic antibody (ANCA), and antinuclear antibodies (ANA) were all unrevealing. An electrocardiogram was normal. Computed tomography (CT) of the head and cervical spine were normal, but magnetic resonance imaging (MRI) of the brain and complete spine revealed findings consistent with discitis, osteomyelitis, and epidural abscess with spinal cord compression at C5-C6. CT imaging of the chest, abdomen, and pelvis revealed upper-lobe cavity nodules and bilateral non-enhancing adrenal masses without calcification, consistent with acute adrenal hemorrhage (Figure 1) [18].

![Figure 1](image-url)
The patient was administered broad-spectrum antibiotics, including vancomycin, as well as i.v. fluids. Despite this, his clinical status declined rapidly with hypotension and shock, acute encephalopathy, worsened weakness to include his left upper and lower extremities, with loss of sensation below the clavicle bilaterally, and acute hypoxic respiratory failure. The patient was intubated due to respiratory status and for airway protection and initiated on vasopressor medications. His blood cultures drawn on admission at that time revealed 2/2 bottles positive for gram-positive cocci in clusters, later confirmed to be methicillin-resistant Staphylococcus aureus (MRSA) by drug susceptibility testing. Neurosurgery was consulted and recommended against surgical decompression as it was unlikely to be of clinical benefit due to an already complete cervical cord injury. There were no vegetations visualized on transthoracic echocardiogram (TTE), and a transesophageal echocardiogram unfortunately was not able to be obtained due to failure to pass the esophagus.

Overall gains were made in clinical status over the next few days, with blood cultures clearing and improvements in respiratory and mental status to the point of extubation. The patient’s hypotension persisted for much longer, however, initially requiring 2 pressors on admission. The patient was additionally started on i.v. hydrocortisone 50 mg every 8 h 3 days later after the above CT findings and an 08:00 a.m. serum cortisol measurement of 5.6 µ/dL. Hydrocortisone was continued at the stated dose for 5 days, then slowly tapered and transitioned to prednisone and fludrocortisone. This treatment corresponded with an improvement in blood pressure over the next several days, although the patient still required norepinephrine off and on. As clinical evidence pointed towards resolution of the septic shock and the adrenal insufficiency was being treated, a component of neurogenic shock from the spinal cord injury was considered and the patient was transitioned to long-term midodrine. Although unfortunately not recovering motor function, the patient remained stable for the remainder of his hospital course and completed 8 weeks of i.v. antibiotics for MRSA bacteremia and presumed endocarditis.

### Discussion

The case presented above brings to attention several learning points for clinicians. The first of these is to be aware of the possibility of acute adrenal hemorrhage and adrenal insufficiency as an etiology of refractory shock in *Staphylococcus aureus* infection. The second point is that the classic presentation with coagulopathy and rash typical of meningococcal-associated Waterhouse-Friderichsen syndrome may be absent in non-meningococcal infections [1,2]. The third learning point is that this condition can occur at all ages and multiple different infections, but the majority of known cases occur in children with pneumonia [13-16].

In our patient, *Staphylococcus aureus* was diagnosed on admission blood cultures, and adrenal hemorrhage by CT imaging of the abdomen and pelvis. The diagnosis of acute adrenal insufficiency in critical illness remains challenging, especially with other forms of shock complicating the picture. The Society for Critical Care Medicine released a guideline in 2017 for the diagnosis of critical illness-related corticosteroid insufficiency (CIRCI), suggesting a random serum cortisol level less than 10 µg/dL for a diagnostic threshold to consider steroid replacement [19]. Our patient did meet this criteria, with a serum cortisol level of 5.6 µ/dL. Other referenced studies did not perform adrenal function testing [13-16].

General measures for the treatment of sepsis and Waterhouse-Friderichsen syndrome were provided, including prompt antibiotic therapy, i.v. fluids, vasopressors, and hydrocortisone therapy. Our patient’s shock improved only after initiation of hydrocortisone therapy, although he did still need long-term midodrine for a component of spinal shock from his cervical cord injury. Although our patient survived the illness with severe resultant morbidity, all other referenced patients died as a result of their illness [13-16]. This compares to a mortality rate of 15-50% for Waterhouse-Friderichsen syndrome as a whole [1-2].

Interestingly, our patient did not develop the rash and coagulopathy characteristic of classic meningococcal Waterhouse-Friderichsen syndrome. Although variably present, especially in non-meningococcal infections, these features were in fact reported in all published cases of *Staphylococcus aureus* associated adrenal hemorrhage that cited these clinical characteristics [1,2,8-16]. The other non-specific signs of

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**Figure 1.** Contrast-enhanced computed tomography (CT) imaging of the abdomen and pelvis, revealing bilateral adrenal hemorrhages (arrows).

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Kalinoski T. Waterhouse-Friderichsen syndrome with bilateral adrenal hemorrhage.
Waterhouse-Friderichsen syndrome and adrenal insufficiency, such as weakness, fatigue, nausea, and confusion, overlapped with those already expected for a septic patient.

Similar to meningococcal infection, the majority of the known published cases of Staphylococcus aureus infection with acute adrenal hemorrhage have occurred in children, but there have been a few adult cases [13-16]. The youngest case involved a 2-year-old and the oldest a 34-year-old. One study did not mention the exact ages of all patients, but stated both adults and pediatric cases were involved [14]. The etiology of our patient’s infection was due to i.v. drug use, compared to the pneumonia, cellulitis, and myositis in other known studies [13-16].

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Conclusions

This paper emphasizes the uncommon sequela of Waterhouse-Friderichsen syndrome associated with Staphylococcus aureus bacteremia, previously reported in just a few case studies. As the manifestations of this condition overlap with septic shock and most patients do not receive an autopsy, it is possible that the frequency is underappreciated and its diagnosis requires a high index of suspicion in the critically ill patient.

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