Extreme Pyrexia and Rapid Death Due to *Staphylococcus aureus* Infection: Analysis of 2 Cases

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We describe unusual *Staphylococcus aureus* infections in 2 patients. The infections were characterized by extreme pyrexia and rapid death. Both causative organisms produced a deletion mutant form of toxic shock syndrome toxin–1 and variant enterotoxin C, which may have caused pyrexia and death.

Pyrogens elevate the temperature set point, producing fever, a normal response to human infection. Although it is incompletely understood, fever is a regulated response, as opposed to hyperthermia, for which there is a failure of thermoregulatory mechanisms [1, 2]. Because the febrile response rarely, if ever, produces temperatures exceeding 42°C (107.6°F) [3], diagnoses such as malignant hyperthermia or neuroleptic malignant syndrome, in which there is a failure of thermoregulation, are entertained when temperatures exceed 41°C (105.8°F). Even in severe bacterial infections associated with production of potent pyrogens, such as staphylococcal toxic shock syndrome, temperatures exceeding 41.7°C (106.5°F) are uncommon or do not occur.

We report 2 cases of extreme pyrexia associated with *Staphylococcus aureus* infection that we believe represent a new syndrome most likely related to changes in pyrogenic toxin superantigens (SAgs). The patients had documented temperatures of ≥42.2°C (≥108°F) and unexpectedly rapid deaths. In one case, which did not involve prolonged hypotension, widespread tissue necrosis was seen with no obvious pathophysiologic explanation. Although 1 isolate was methicillin susceptible and 1 was methicillin resistant, they displayed similar SAg production.

**Materials and methods.** *S. aureus* was identified as gram-positive cocci and as catalase and coagulase positive. Production of SAgs (toxic shock syndrome toxin–1 [TSST-1], staphylococcal enterotoxin B, and staphylococcal enterotoxin C [SEC]) was assessed by antibody-based double immuno-diffusion [4]. PCR for genes for TSST-1 (*tstH*), staphylococcal enterotoxin B (*seb*), and SEC (*sec*) was performed [5]; primers listed in table 1.

**Case reports.** Patient 1 was a previously healthy 39-year-old woman who presented to an outside hospital with back, hip, and abdominal pain, which had been gradually worsening over the prior week. Fever, nausea, and vomiting had begun in the 24–48 h before presentation. A WBC count of 14 × 10^9^ cells/μL and a creatinine level of 2.9 mg/dL were noted. CT revealed edema of the left psoas muscle that was thought to be a hemorrhage, and the patient was transferred to our institution (University of South Dakota).

Upon questioning, the patient and family related a history of a recent fall and heavy use of ibuprofen for pain. Her temperature was 37°C (98.6°F), her pulse was 120 beats/min, her respiration rate was 20 breaths/min, her systolic blood pressure was 135 mm Hg, and her oxygen saturation was 99% on room air. Her WBC count was 10.4 × 10^9^ cells/μL, with mild lymphopenia and a slight left shift. The hemoglobin concentration was 12.4 g/dL, and the platelet count was platelets/3249 L. The blood urea nitrogen level was 43 mg/dL, and the creatinine level was 2.0 mg/dL. The international normalize ratio was 1.3, and the total creatine kinase level was 1185 U/L. Chest radiography revealed no abnormalities, and an additional CT revealed ileopsoas region abnormalities, which were consistent with acute left retroperitoneal and pelvic hematoma. The patient was admitted to the intensive care unit, and she began receiving intravenous fluids, vancomycin, and ceftriaxone.

The patient remained hemodynamically stable except for some sinus tachycardia, which was treated with intravenous metoprolol. Her oxygen requirements increased, and she required intubation and mechanical ventilation 11 h after admission. Her temperature increased steadily after hospital admission. Despite having received acetominophen, methylprednisolone, and application of a cooling blanket, her temperature increased to 41°C (106.5°F), determined rectally, 13 h after admission. Because she received succinylcholine during intubation earlier in the day, dantrolene was administered without effect. Subsequently, she became completely obtunded, and her systolic blood pressure...
but was not recorded. Admission. The patient's peak temperature may have been higher with intermediate susceptibility to fluoroquinolones and resistance to erythromycin. The organisms produced TSST-1 (6 m/mL in vitro) and SEC (6 m/mL), as determined by antibody tests [4]. PCR indicated that the strains contained seb and a deletion mutant of tstH [5]. Autopsy revealed acute kidney syndrome toxin–1.

Two blood cultures revealed methicillin-resistant S. aureus with intermediate susceptibility to fluoroquinolones and resistance to erythromycin. The organisms produced TSST-1 (6 μg/mL in vitro) and SEC (6 μg/mL), as determined by antibody tests [4]. PCR indicated that the strains contained seb and a deletion mutant of tstH [5]. Autopsy revealed acute kidney tubular and early hepatocellular necrosis, as well as left retroperitoneal cellulitis with associated fat necrosis. Large colonies of gram-positive cocci were noted along the peritoneal surface in the left retroperitoneum.

Patient 2 was a 68-year-old man who presented to the emergency department with shortness of breath, which had been worsening over the prior 48 h. He had an extensive history of tobacco use but had quit 7 years previously. He had received a diagnosis of chronic obstructive pulmonary disease (COPD) and was using inhalers. His temperature was 37.8°C (100°F), determined rectally, 19 h after admission. The patient’s family declined autopsy. Resuscitative efforts were initially successful, with the systolic blood pressure increasing to 100 mm Hg. However, the patient again became hypotensive, and despite maximal vasopressor support, further resuscitative efforts were unsuccessful; the patient died 20 h after hospital admission. The patient’s family declined autopsy.

Tracheal aspirate culture yielded heavy growth of methicillin-resistant S. aureus, with intermediate susceptibility to fluoroquinolones, whereas the results of cultures of blood samples obtained at the time of admission remained negative. The S. aureus isolate produced TSST-1 (6 μg/mL in vitro) and SEC (6 μg/mL) [4]. PCR indicated the presence of seb and a deletion mutant of tstH [5].

Discussion. Morbidity and mortality due to S. aureus are not unexpected. These 2 cases, however, exhibit unique features that represent departures from typical S. aureus disease. Of note, there were documented temperatures of ≥42.2°C (≥108°F).
High temperatures can be seen with bacterial infection. Nonetheless, elevations to this degree are unusual. Autopsy performed on the first patient revealed widespread tissue necrosis with no obvious pathophysiologic correlate. Hyperthermia can be fatal, inducing widespread cytotoxicity, and could explain these findings [6]. However, temperatures of 42°C (107.6°F) have been deliberately induced in humans without ill effects [7]. Thus, it is more likely that additive effects of hyperthermia, sepsis, and SAgs are the cause of the observed cytotoxicity. The second patient had a temperature of 42.3°C (108.2°F), despite having received substantial doses of methylprednisolone, and refractory hypotension without concomitant bacteremia. These are not typical features of S. aureus infection and suggest altered patterns or effects of SAgs.

We evaluated the causative organisms for SAgs; both were found to be positive for TSST-1 and SEC by antibody tests [4]. This SAg combination is observed in 15% of toxic shock syndrome isolates [8]. However, our studies suggest these stains, which appear as CDC USA300 [9], produce a deletion mutant of TSST-1 and variant SEC. PCR followed by sequencing [5] indicates the encoded TSST-1 has a deletion encompassing its N-terminal half; the mutant protein has a predicted molecular weight of 13,000 (shortened by 72 amino acids), compared with 22,000 for native TSST-1. This deletion disrupts the major histocompatibility complex II-binding domain [10], despite the toxin maintaining antibody reactivity. Part of the T cell receptor–binding site is conserved [10]. Administration of cell-free culture supernates (2 mL/rabbit) intravenously was pyrogenic (mean rectal temperature at 3–4 h ± SD, 42.5°C [108.5 °F] ± 0.15 °C), rapidly and uniformly lethal (after 5–6 h, 6 of 6 succumbed), but fever and lethality were neutralized by immunization or passive antibodies against native TSST-1 (0 of 6 succumbed; P < .001, by Fisher’s exact test, compared with controls). This suggests that these strains produce a mutant of TSST-1 that increases virulence, inducing extreme pyrexia and lethality. We do not know if activity occurs through superantigenicity or novel effects such as direct neurotoxicity; the mutant retains 60% of native TSST-1 superantigenicity.

We have not studied the SEC variation, and we have not assessed SEC activity in rabbits. However, the SEC may be less important in rabbits, because antibodies against TSST-1 provide complete protection from culture supernate challenge. PCR indicates the strains lack sec, although antibody tests suggest SEC protein production. PCR indicates the strains contain seb, which is highly related to sec, but antibody tests are negative for staphylococcal enterotoxin B. On the basis of the greater specificity of antibody reactivity versus PCR, we suggest that the strains make a variant SEC.

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