

Serious Complications from *Staphylococcal aureus* in Atopic Dermatitis

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Abstract: Colonization with *Staphylococcal aureus* is markedly more frequent in individuals with atopic dermatitis (AD) than in unaffected individuals. Chronic scratching leads to worsening of an existing defect in the epidermal barrier, which can allow *S. aureus* invasion into the bloodstream and subsequent systemic infections. We report two unusual cases of systemic illness in individuals with AD. One developed infective endocarditis followed by a stroke and the other developed septic arthritis and osteomyelitis. We performed an extensive literature review of reported systemic complications caused by *S. aureus* in patients with AD. Although reports are rare, practitioners should be aware of these important, albeit unlikely, complications of staphylococcal superinfections in individuals with AD.

Atopic dermatitis (AD) is the most common chronic inflammatory skin condition in children. Colonization by *Staphylococcal aureus* is a common feature of AD (1). Although colonization is highest on lesional skin, colony counts are also often high on clinically normal skin of patients with AD, who have epidermal barrier abnormalities, including defects in filaggrin and low antimicrobial peptide levels, which can cause immune dysregulation within the skin and may help explain the unique predisposition of colonization with *S. aureus* in skin with AD (2,3). *S. aureus* colonization may progress to cause secondary cutaneous and soft tissue infections such as impetiginization, widespread folliculitis, cutaneous abscesses, and cellulitis (4). Although skin and soft tissue infections occur frequently, there are sporadic case reports describing cutaneous *S. aureus* colonization leading to more invasive infections such as

bacteremia, sepsis, endocarditis, osteomyelitis, septic arthritis, pneumonia, and ocular infections.

Herein we provide the results of our literature review to summarize the rare noncutaneous and non-soft tissue *S. aureus* systemic infections reported in patients with AD. Although systemic infections with *S. aureus* in AD are uncommon, clinicians should be aware of these potential complications because of their severity (Table 1).

In our experience at the Children's Hospital of Michigan and Henry Ford Health System, the systemic infections we address are exceptionally rare, but over a period of just 2 months we were consulted in the intensive care unit on two children admitted with severe AD and systemic infections. One patient was a 17-year-old girl with severe uncontrolled AD who had presented with status epilepticus to another hospital and was found to have septic emboli and

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TABLE 1. *Systems at Risk for Staphylococcus aureus Infection in Patients with Atopic Dermatitis*

System	Complication
Cardiovascular	Native valve endocarditis (11–15), cerebrovascular emboli (10), mediastinitis (16), postoperative infection (16)
Osteoarticular	Osteomyelitis (18,19), septic arthritis (18), discitis (7)
Pulmonary	Necrotizing pneumonia (22–24), lung abscesses (24), pneumonia (24)
Ocular	<i>S. aureus</i> colonization in conjunctival sac and eyelid margin (25)
Hematogenous	Bacteremia (5), septic shock (6)

methicillin-resistant *S. aureus* (MRSA) endocarditis. The transferring institution did not take cultures from her severely atopic skin before starting systemic antibiotics. The patient had no known history of intravenous drug use and no evidence of such on examination. Her course was additionally complicated by an embolic stroke and pericarditis. The stroke caused her to have residual speech and motor deficits and she had to undergo mitral valve replacement because of valvular damage from the infective endocarditis. After a prolonged inpatient admission, she was discharged to an outpatient rehabilitation center. A neurology clinic note several months later listed many residual functional deficits. This is the only mention of her being seen in follow-up and her chart lists her as deceased. Additional information to explain the circumstances of her death was absent from her medical records.

The other patient was an 8-year-old girl with poorly controlled, severe AD who presented with fever, marked left shoulder swelling, and excruciating pain. Her mother reported pus bumps on the skin and worsening of her eczema that started weeks before the onset of her joint symptoms. The orthopedic team performed a diagnostic joint aspiration followed by irrigation and debridement. A diagnosis of MRSA septic arthritis and associated osteomyelitis was made. She was given 3 weeks of intravenous clindamycin followed by 3 weeks of oral clindamycin, which led to improvement. Nine weeks later she presented again with a 1-week history of recurrent pain and pus drainage from the same site. Extensive myositis and a large abscess were seen on ultrasound and magnetic resonance imaging (MRI). She was taken to the operating room on three separate occasions for irrigation, incision and drainage, and delayed closure once cultures were negative. One of the cultures grew clindamycin-resistant MRSA, and she was treated with intravenous vancomycin. She was discharged to

continue home infusions. Because of difficulty maintaining trough levels, the vancomycin required dosing every 6 hours, but the family was unable to maintain this dosing regimen. She was changed to dactomycin intravenously once daily to complete 6 weeks total of intravenous antibiotics. MRI performed at the end of her treatment course showed mild remaining myositis, and a 10-day course of oral Bactrim was given. More than 1 year later, no new or residual infections had been noted during her multiple admissions for status asthmaticus, although she did not follow-up with dermatology.

Although we could not confirm that either of these patients developed systemic infections directly associated with their AD, we suggest that the skin colonization of *S. aureus* was the most likely source. In both patients, the families reported a history of poorly controlled AD and poor adherence to skin care. In both cases, dermatology was consulted late in the patients' hospitalizations, well after they had been treated for their infections. By raising awareness of the potential systemic hazards with poor control of superinfected AD skin, we hope to help practitioners gain better insight into the importance of managing *S. aureus*. We encourage early dermatology consultation for patients who may be at risk of developing extracutaneous infections.

BACTEREMIA

Hoeger et al (5) reported two cases of *S. aureus* bacteremia in patients with AD. They proposed that intense, chronic scratching of already dry, fissured skin led to invasion of *S. aureus* into the bloodstream. *S. aureus* bacteremia is reported to lead to severe complications such as septic shock and cardiac arrest (6) and may cause seeding of the organism in other organs, which can lead to fatal infections and organ dysfunction and require aggressive therapy or surgical intervention.

Carr et al (7) reported the case of a 19-year-old man with AD and no identifiable immunodeficiency who presented with recurrent invasive *S. aureus* infections over 5 years. The infections included osteomyelitis, discitis, bacteriuria, native valve endocarditis requiring valve replacement, and a few months later, prosthetic valve endocarditis complicated by cerebrovascular emboli. Although the infections in this case cannot be irrefutably linked to the patient's AD, no source of *S. aureus* was identified other than the colonization identified on his atopic skin.

S. aureus infections may exacerbate AD. Eczematous skin refractory to topical steroids can be a clue to

superficial or deep-seated infections. This phenomenon may be due to the superantigens that *S. aureus* releases. The superantigens activate T-cells, which in turn secrete cytokines that mediate inflammation in the skin (8). Flared AD skin tends to show improvement once the invasive *S. aureus* infection is treated (9). Although rare, *S. aureus* bacteremia should be considered in the differential diagnosis of fever and worsening clinical appearance in patients with AD. If bacteremia is suspected, prompt examination and aggressive treatment are necessary to prevent severe complications.

CARDIOVASCULAR

Native valve endocarditis caused by *S. aureus* often leads to the development of large mobile vegetations. These vegetations make preservation of the valve difficult, and many patients require prosthetic valve replacement. Embolic events and neurologic complications are, in general, more common with *S. aureus* endocarditis than endocarditis caused by other organisms (10). There are several reports discussing the causal relationship between AD and *S. aureus* native valve infective endocarditis in children (11–15).

In addition to cardiac complications, which may arise from infected skin through bacteremia, Fukunaga et al (16) explained that it is important for cardiac surgeons to be aware that skin with AD is frequently colonized with *S. aureus*. During open-heart surgery, direct exposure of the bone marrow to skin with AD colonized with *S. aureus* can result in mediastinitis. To decrease the risk of mediastinitis, Fukunaga et al (16) recommended thoracotomy over median sternotomy as the preferred surgical approach to minimize exposed bone marrow in adults with AD. They also recommended that adequate skin care be used to control skin lesions for individuals with AD before open heart surgery if possible.

Physicians should also be cautious when prescribing systemic medications that cause leukopenia and may increase susceptibility to bacterial sepsis in patients with AD. Satchell et al (17) described a case of *S. aureus* septicemia complicated by native valve endocarditis and septic vegetations requiring valve replacement in an adult with severe AD recently started on mycophenolate mofetil for her uncontrolled skin disease. The authors proposed invasion of *S. aureus* from eczematous skin in a newly immunosuppressed patient was the cause of the bacteremia.

We suggest that severe AD should be considered a risk factor for developing *S. aureus* endocarditis,

especially if the patient is immunosuppressed. Also, preoperative precautions should be initiated in individuals with AD when cardiac surgery is needed.

OSTEOARTICULAR

Osteoarticular complications in AD are rare, although there have been scattered reports of osteomyelitis and septic arthritis in association with AD (18). Sharma (9) reported a case of *S. aureus* osteomyelitis of the right fibula in a patient with AD. Because the *S. aureus* cultured from the skin and the involved bone showed similar antibiotic sensitivities, it was concluded that the probable source of bone infection was the skin.

Boiko et al (19) reported three cases of *S. aureus* osteomyelitis of the distal phalanges of the hands in individuals with AD. Because osteomyelitis of the phalanges in children is not ordinarily spread hematogenously, they postulated that the osteomyelitis seen in these cases was secondary to trauma. Although they could not prove their theory, they proposed that the mechanical trauma with elevation of the nail bed from the retained subungual debris led to a closed-space collection of bacteria and keratin. This may have formed the initial nidus of infection and led to development of a subungual soft tissue abscess, which may have then penetrated the nail bed and spread through direct extension into the bone.

Although bone involvement was severe radiologically in the cases of Boiko et al (19) and Sharma et al (9), the patients did not have systemic symptoms other than mild edema of the skin overlying the bone (19). Management of the osteomyelitis using systemic antibiotics cured the osteomyelitis and improved the AD, which was not responding well to topical steroids. This finding emphasizes the importance of noticing whether soft tissue swelling overlying a bone occurs, because it may be the only sign that these patients will develop.

PULMONARY

Necrotizing pneumonia secondary to Panton–Valentine leukocidin (PVL)–producing *S. aureus* has been reported to occur in individuals with AD. PVL is a pore-forming cytokine that can cause the destruction of leukocytes. It is produced by <5% of *S. aureus* associated with skin and soft tissue infections (20–22). Heelen et al (23) reported the case of three brothers with AD complicated by PVL-producing *S. aureus* skin infections. Their 21-month-old sister subse-

quently developed acute hemorrhagic bronchopneumonia from PVL-positive *S. aureus*. Even though their sister had no reported history of AD, the contagious organism on her brothers' skin may have led to the development of her pneumonia. It is unclear whether hematogenous spread of *S. aureus* to the lungs causes necrotizing pneumonia with associated focal skin infection or if its transmission is airborne (24).

Gillet et al (24) reported *S. aureus* sepsis in a 17-year-old individual that resulted in the development of multiple lung abscesses and fulminant staphylococcal pneumonia. A preexisting PVL-positive cutaneous furuncle was the only identifiable cause (24). Although the patient did not have AD, Felton et al (22) reported individuals with AD with PVL-positive *S. aureus* cutaneous infections. If individuals with AD develop cutaneous infections such as furuncles or abscesses from the PVL-positive *S. aureus*, lung abscesses and necrotizing pneumonia could arise.

OCULAR

In addition to cutaneous colonization by *S. aureus*, individuals with AD have a higher incidence of ocular colonization of *S. aureus* than those without. *S. aureus* was found in the conjunctival sac and eyelid of 67% of individuals with AD, compared with 6% of those without (25). It is highly likely that this high rate of colonization of *S. aureus* in the conjunctival sac and eyelid margin is related to its colonization of the skin.

Nakata et al (25) noted that we must pay attention to the uniquely high rate of *S. aureus* in the eyes of atopics, especially in patients that require ocular surgery. It is recommended to perform bacterial isolation before surgery and use appropriate antibiotics postoperatively. Also, the sterility of the intraoperative field during ocular surgery should be meticulously maintained to reduce postoperative ocular infections with *S. aureus* in AD patients (25).

CONCLUSION

Because individuals with AD are at greater risk of various types of infections with *S. aureus*, vigilance on the part of physicians and patients is necessary. In addition to treating eczematous lesions, we recommend proactively addressing the bacteria on the skin by instituting dilute bleach baths and possibly using intermittent intranasal mupirocin. Consistent use of dilute bleach baths is an effective way to manage *S. aureus* colonization and decrease the severity of

AD. Huang et al (26) demonstrated that dilute bleach baths with intermittent intranasal mupirocin application was helpful in the treatment of moderate to severe AD. When infections occur, it is imperative to recognize that most *S. aureus* in individuals with AD are methicillin sensitive, according to a study performed at Rady Children's Hospital in San Diego (27). As long as the patient does not have risk factors for MRSA, cephalosporins should be considered the first-line oral antibiotic in mild skin and soft tissue superinfections in AD, but if patients are known to carry methicillin-resistant strains, appropriate antibiotics should be considered.

Systemic infections in patients with AD are unlikely. Despite their uncommon occurrence, practitioners should be aware of the potential complications reviewed in this article and maintain surveillance. The prevention of skin and soft tissue infections should be emphasized with patients, and if they occur, we recommend prompt treatment, which will help prevent further invasion into the bloodstream and viscera and thus prevent systemic complications with high morbidity and mortality.

REFERENCES

1. Higaki S, Morohashi M, Yamagishi T et al. Comparative study of staphylococci from the skin of atopic dermatitis patients and from healthy subjects. *Int J Dermatol* 1999;38:265–269.
2. Boguniewicz M, Leung DY. Insights into atopic dermatitis and implications for management of infectious complications. *J Allergy Clin Immunol* 2010;254:4.
3. Baker BS. The role of microorganisms in atopic dermatitis. *Clin Exp Immunol* 2006;144:1–9.
4. Elias P, Yutaka H, Williams M. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol* 2008;121:1337–1343.
5. Hoeger PH, Ganschow R, Finger G. Staphylococcal septicemia in children with atopic dermatitis. *Pediatr Dermatol* 2000;17:111–114.
6. Hon KL, Nip SY, Cheung KL. A tragic case of atopic eczema: malnutrition and infections despite multivitamins and supplements. *Iran J Allergy Asthma Immunol* 2012;11:267–270.
7. Carr T, Avila P. Recurrent deep-seated *Staphylococcal aureus* infections of unclear etiology. *J Clin Immunol* 2011;31:S29.
8. Strange P, Skov L, Lisby S et al. Staphylococcal enterotoxin B applied on intact normal and intact atopic skin induces dermatitis. *Arch Dermatol* 1996;132:27–33.
9. Sharma AK. Atopic dermatitis and *Staphylococcus aureus*-induced osteomyelitis—a peculiar association in a case. *Pediatr Dermatol* 1996;14:453–455.
10. Harada M, Nishi Y, Tamura S et al. Infective endocarditis with a huge mitral vegetation related to atopic

- dermatitis and high serum level of infection-related antiphospholipid antibody. *J Cardiol* 2003;42:135–140.
11. Benenson S, Zimhony O, Dahan D et al. Atopic dermatitis—a risk factor for invasive *Staphylococcus aureus* infections: two cases and review. *Am J Med* 2005;118:1048–1051.
12. Yamamoto T, Yodogawa K, Wakita S et al. Recurrent prosthetic valve endocarditis caused by *Staphylococcus aureus* colonizing skin lesions in severe atopic dermatitis. *Intern Med* 2007;46:571–573.
13. Kobayashi H, Sugiuchi R, Tabata N et al. Guess what! Acute infectious endocarditis with Janeway lesions in a patient with atopic dermatitis. *Eur J Dermatol* 1999;9:239–240.
14. Grabczynska SA, Cerio R. Infective endocarditis associated with atopic eczema. *Br J Dermatol* 1999;140:1193–1194.
15. Pike MG, Warner JO. Atopic dermatitis complicated by acute bacterial endocarditis. *Acta Paediatr Scand* 1989;78:463–464.
16. Fukunaga N, Yuzaki M, Shomura Y et al. Clinical outcomes of open-heart surgery in patients with atopic dermatitis. *Asian Cardiovasc Thorac Ann* 2012;20:137–140.
17. Satchell AC, Barnetson RS. Staphylococcal septicaemia complicating treatment of atopic dermatitis with mycophenolate. *Br J Dermatol* 2000;143:202–203.
18. Kitamura S, Nakayama Y, Shirai Y et al. Septic arthritis of the hip associated with atopic dermatitis. A case report. *J Nippon Med Sch* 2000;67:464–467.
19. Boiko S, Kaufman RA, Lucky AW. Osteomyelitis of the distal phalanges in three children with severe atopic dermatitis. *Arch Dermatol* 1988;124:418–423.
20. Pouessel G, Ythier H, Carpentier O et al. Childhood pustular psoriasis associated with Pantone-Valentine leukocidin-producing *Staphylococcus aureus*. *Pediatr Dermatol* 2007;24:401–404.
21. Gauduchon V, Werner S, Prevost G et al. Flow cytometric determination of Pantone-Valentine leukocidin S component binding. *Infect Immun* 2001;69:2390–2395.
22. Felton S, McMullen E, Ghura V et al. Outbreak of Pantone-Valentine leukocidin-positive *Staphylococcus aureus* in dermatology inpatients in the UK: an escalating phenomenon? *J Am Acad Dermatol* 2013;68:AB123.
23. Heelan K, Murphy A, Murphy LA. Pantone-Valentine leukocidin-producing *Staphylococcus aureus*: report of four siblings. *Pediatr Dermatol* 2012;29:618–620.
24. Gillet Y, Issartel B, Vanhems P et al. Association between *Staphylococcus aureus* strains carrying gene for Pantone-Valentine leukocidin and highly lethal necrotizing pneumonia in young immunocompetent patients. *Lancet* 2002;359:753–759.
25. Nakata K, Inoue Y, Harada J et al. A high incidence of *Staphylococcus aureus* colonization in the external eyes of patients with atopic dermatitis. *Ophthalmology* 2000;107:2167–2171.
26. Huang JT, Abrams M, Tlougan R et al. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatric* 2009;123:808–814.
27. Matiz C, Tom WL, Eichenfield LF et al. Children with atopic dermatitis appear less likely to be infected with community acquired methicillin-resistant *Staphylococcus aureus*: the San Diego experience. *Pediatr Dermatol* 2011;28:6–11.