Impetigo/Staphylococcal Scalded Skin Disease

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Bacterial skin infections are among the most common skin diseases in children. These encompass a range of cutaneous manifestations from localized (bullous impetigo) to systemic (staphylococcal scalded skin disease [SSSS]). The most common pathogen in both nonbullous and bullous impetigo is *Staphylococcus aureus*. Another important pathogen causing nonbullous impetigo is group A β-hemolytic *Streptococcus*. SSSS specifically refers to a spectrum of skin diseases induced by the exfoliative toxins of S *aureus*. The most common pathogen implicated in their pathophysiology is *S aureus,* which is a gram-positive coccus and can commonly colonize the nose, perineum, eyes, axillae, umbilicus, and wound sites.

Impetigo frequently involves children younger than 6 years, accounting for approximately 10% of skin problems observed in pediatric clinics. SSSS is a rare blistering manifestation affecting mainly neonates and young children. Impetigo is an extremely contagious infection that can spread quickly via direct person-to-person contact or through fomites, and its peak incidence is in the summer months. Primary impetigo can result from direct bacterial involvement of the previously normal skin, whereas secondary impetigo is caused by a disruption in the skin barrier that allows the bacteria to adhere, invade, and establish an infection. Causes of secondary impetigo include minor skin trauma secondary to abrasions, cuts, or insect bites or skin infections due to herpes simplex virus or varicella zoster virus. Colonization of the nasopharynx, axillae, and perineal skin with *S aureus* increases the risk of developing staphylococcal infections. Impetigo is classified as nonbullous or bullous. Whereas nonbullous impetigo is caused by the direct insult of *S aureus,* bullous impetigo and SSSS are caused by the exfoliative toxin released by *S aureus*. Exfoliative toxins, also known as epidermolytic toxins A and B, expressed by phage group II, produce bullae by binding to the desmosomal protein desmoglein 1, cleaving its extracellular domain, which causes splitting of the desmosomes. For bullous impetigo, the toxin creates bullae locally at the site of infection, so blood cultures would be negative in these children. In SSSS, these toxins circulate throughout the body, causing blisters at sites distant from the infection. Hematogenous dissemination of the same toxin usually originates from the nasopharynx, umbilicus, or perineum in neonates and young children, whereas in adults the lungs (staphylococcal pneumonia) or the bloodstream (bacteremia) can be the infectious site.

Clinically, nonbullous impetigo presents as erythematous macules that rapidly evolve into a vesicle or pustule that is short-lived and leaves behind superficial erosions with a typical honey-colored yellow crust that can progress to have rapid direct extension of infection to the surrounding skin. Bullous impetigo presents as small vesicles that enlarge into 1- to -cm superficial bullae that can leave behind

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a collarette of scale with a little surrounding erythema. Lesions most commonly involve the face, particularly the nose and mouth; however, the trunk, buttocks, perineum, axillae, and extremities can also be involved. Both types typically resolve within 2 to 3 weeks without scarring.

SSSS affects young infants and children because they have decreased renal toxin clearance and, in some cases, lack toxin-neutralizing antibodies. Outbreaks among neonates usually occur secondary to parents or health-care workers being carriers of a toxigenic strain of *S aureus*. Rarely it can also affect adults with immunodeficiency or renal failure. Clinically, SSSS presents with a prodrome of malaise, fever, irritability, and severe tenderness of the skin that can be associated with erythroderma. This is quickly followed by the formation of large, flaccid, fluid-filled bullae in the superficial epidermis that quickly rupture to leave extensive areas of denuded skin. The Nikolsky sign is a clinical sign that is elicited by applying horizontal pressure to the skin, resulting in extension of the blister and separation of the epidermis of the adjacent skin, and is positive in SSSS. Note that there is absence of mucosal involvement, unlike other blistering conditions of the skin, such as Stevens-Johnson syndrome. Patients have characteristic radial fissuring and crusting of the perioral and periocular skin. The erythrodermic skin is followed by superficial desquamation, leaving behind moist skin and thin crusting. Scaling and desquamation can continue for the next 3 to 5 days, followed by reepithelialization without scarring. The diagnosis of impetigo and SSSS is usually made clinically, which can be supported by the presence of *S aureus*. In bullous impetigo, culturing exudate beneath the crust or fluid from an intact bulla can help make the diagnosis. In SSSS, culturing the bullae will not yield the causative bacteria because the source of infection is distant from the blistering. Therefore, it is important to culture exudates from the nares, umbilical, and perineum, in addition to blood cultures, to guide antibiotic drug treatment. According to an updated Cochrane Review in 2012 on impetigo interventions, there was no clear evidence in comparative effectiveness studies whether oral or topical antibiotic drug treatments were most effective. The choice of treatment is affected by the extent of skin involvement, other comorbidities such as eczema, the patient's immune status, and the likelihood of methicillin-resistant *S aureus* (MRSA). Superficial lesions of impetigo can be treated with topical antibiotic agents such as mupirocin 2% cream or ointment, retapamulin 1% ointment, and fusidic acid (not available in the United States). Affected areas can also be cleaned with topical disinfectants such as saline, hexachlorophene, povidone iodine, and chlorhexidine. Removing crusts with wet dressings can also help in faster clearance. Mupirocin ointment has been shown to be at least as effective as oral antibiotics when the extent of the disease is limited. However, oral antibiotic drug therapy can be used for impetigo with large bullae. Erythromycin and penicillin were standard treatments in the past, but because of emerging drug resistance, they are no longer routinely used. Oral antibiotic options include cephalexin, clindamycin, augmentin, doxycycline, and trimethoprim/sulfamethoxazole. If MRSA infection is suspected, initial treatment with trimethoprim/sulfamethoxazole, clindamycin, or a tetracycline such as doxycycline or minocycline is recommended pending culture results.

Patients with SSSS require hospitalization and parenteral antibiotic drug therapy. The first-line antibiotics are intravenous antistaphylococcal antibiotics such as nafcillin, oxacillin, flucloxacillin, cloxacillin, and dicloxacillin until cultures and sensitivities are available to guide antibiotic drug therapy. Clindamycin is also often added in cases of severe SSSS as an adjunctive therapy to reduce bacterial toxin production, because it acts on the ribosome of the bacteria, thereby inhibiting protein synthesis. These patients may also need symptomatic support if they have extensive areas of the skin involved (denuded) because they are susceptible to poor temperature control, extensive fluid losses, and secondary infection, which can be complicated by sepsis and respiratory distress. In severe cases when patients are not improving and MRSA is suspected, vancomycin therapy should be started. Identification and decolonization of *S aureus* carriers can also be beneficial to prevent recurrence. The carriage from the nose contains strains of *S aureus* in 35% of the population, which can vary depending on age and race. In the event of an outbreak of SSSS correlated with such carriers, topical therapy should be continued with mupirocin as adjunct therapy at the site of blisters in an attempt to eradicate colonization.

Typically patients are discharged after 6 to 7 days but are instructed to continue antibiotic drug therapy for a total of 10 to 14 days. Usually SSSS resolves in 10 to 14 days without scarring. The mortality rate is 3% in children but can be greater than 50% in adults.

COMMENT: The breadth of manifestations attributable to *S aureus* infections, which can range from common impetigo to less common SSSS, is fascinating and due to both

characteristics of the infecting organism and also the characteristics of the host as outlined in this *In Brief*. Research has informed us in cases of localized impetigo to use topical antibiotics and hence to avoid potential adverse effects from systemic antibiotics and also to minimize the development of antibiotic resistance. However, more research is needed to identify ways to quickly differentiate SSSS from other diseases with bullous formation and skin disruption, such as drug-induced toxic epidermal necrolysis, because the treatment differs. Also, research further investigating the mechanisms of the toxins and development of a potential antitoxin may benefit patients for whom the morbidity and mortality from SSSS may be high.

– Janet Serwint, MD
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