

REVIEW ARTICLE

Staphylococcal scalded skin syndrome: diagnosis and management in children and adults

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Abstract

Staphylococcal scalded skin syndrome is a potentially life-threatening disorder caused most often by a phage group II *Staphylococcus aureus* infection. Staphylococcal scalded skin syndrome is more common in newborns than in adults. Staphylococcal scalded skin syndrome tends to appear abruptly with diffuse erythema and fever. The diagnosis can be confirmed by a skin biopsy specimen, which can be expedited by frozen section processing, as staphylococcal scalded skin syndrome should be distinguished from life threatening toxic epidermal necrolysis. Histologically, the superficial epidermis is detached, the separation level being at the granular layer. The diffuse skin loss is due to a circulating bacterial exotoxin. The aetiological exfoliating toxin is a serine protease that splits only desmoglein 1. The exfoliative toxins are spread haematogenously from a localized source of infection, causing widespread epidermal damage at distant sites. Sepsis and pneumonia are the most feared complications. The purpose of this review is to summarize advances in understanding of this serious disorder and provide therapeutic options for both paediatric and adult patients. Recent epidemiological studies have demonstrated that paediatric patients have an increased incidence of Staphylococcal scalded skin syndrome during the summer and autumn. Mortality is less than 10% in children, but is between 40% and 63% in adults, despite antibacterial therapy. Previously, intravenous immunoglobulin had been recommended to combat Staphylococcal scalded skin syndrome, but a recent study associates its use with prolonged hospitalization.

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Introduction

Staphylococcal scalded skin syndrome (SSSS) has an estimated incidence in the general population between 0.09 and 0.56 cases per million inhabitants, 10 times lower than the incidence of toxic epidermal necrolysis.^{1,2} However, its incidence in infants has been reported as high as 250 per million in the Czech Republic, a figure derived from a paediatric dermatologist specifically evaluating every infant for this disorder.³ The condition is caused by certain strains of *Staphylococcus aureus* that release serine protease exfoliate toxins that cleave desmosomal cadherins, specifically desmoglein 1, in the superficial epidermis, resulting in destruction of cell–cell adhesion and creating blistering and denuding of the skin.^{4,5} SSSS has a mortality rate of

3.6–11% in children.^{6,7} However, those adults affected by SSSS have a 40–63% mortality rate, perhaps due to an underlying comorbidity.¹ We present an update on the current understanding and treatment of SSSS in both children and adults.

History

The connection between SSSS and *Staphylococcus aureus* (*S. aureus*) was initially proposed in 1891.⁷ It was not until 1956 that Alan Lyell, an eminent British dermatologist, described four patients with ‘a toxic eruption, which closely resembles scalding’.^{8,9} The connection to *S. aureus* came in 1967, when Edmund Lowney described children that were culture positive for *S. aureus* who displayed the ‘scalded skin’ appearance.¹⁰ In 1970, the toxins which are responsible for the exfoliation were isolated.¹¹ It is now known that phage lytic groups of *S. aureus* produce exfoliative toxins to cause SSSS.^{12,13} In 1972, the first case of SSSS was reported in a patient greater than 18 years of age.¹⁴

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Since that time, several hospitals have found the incidence of SSSS among children to be on the rise.^{15–17}

Pathophysiology

S. aureus carriage is ascending in the general population. Although most *S. aureus* strains are methicillin sensitive, there is an increase in methicillin-resistant bacteria causing SSSS.^{2,18–20} *S. aureus* releases multiple enzymes and toxins, yet only 5% of *S. aureus* human isolates produce the exfoliative toxins A and B (ETA, ETB) that cause SSSS.^{5,21} Persistent nasal carriage of strains with the *fnbB* gene may be responsible for an enhanced risk of infection.²²

Staphylococcal aureus of phage group II, types 71 and 55/71, release an exfoliative toxin. The toxin is disseminated haematogenously, producing widespread skin involvement.²³ ETA and ETB are atypical glutamic acid specific trypsin-like serine proteases which collect in the skin.²³ As the exfoliative toxin (ET), a protease, accumulates in the skin, it digests desmoglein 1 (Dsg1), a desmosomal cadherin involved in keratinocyte cell-to-cell adhesion.^{24,25} With loss of Dsg1 there is a deterioration of keratinocyte-to-keratinocyte adhesivity in the stratum granulosum, resulting in bullae formation and denudation.^{24,26}

Risk factors

SSSS can occur at any age but most commonly is evident in children less than 5 years of age, occurring equally in children and adult males and females. There is also an increased paediatric incidence in summer and autumn months.² Two hypotheses on why children have a higher incidence of SSSS are that either they have not yet developed protective antibodies against the staphylococcal toxins or their kidneys are unable to excrete the exfoliative toxin.^{27,28} In adults the greatest risk factor is an underlying illness, especially renal disease, which accounts for a mortality rate greater than 60%.^{26,29} Currently, 46.8% of adults over 70 years of age have chronic kidney disease.³⁰ A suppressed immune system, whether from renal failure, diabetes mellitus or human immunodeficiency virus (HIV) infection, results in an inability to both excrete *S. aureus* exotoxin and to produce antibodies to the exfoliative toxin. Patients undergoing haemodialysis are at risk of SSSS due to infection by *S. aureus* via vascular access port, an inability to excrete ET, and the immunological deficits that accompany renal failure.³¹ Of the two exotoxins that are firmly linked to producing SSSS, ETA and ETB, the latter appears to be the more virulent. In cases of adults without immunosuppression developing SSSS, it is likely that they contracted strains of *S. aureus* with the *etb* gene which encodes virulent exotoxin ETB.³²

Clinical features in children

In children SSSS is first evident with a prodrome of irritability, malaise and fever. Even before the initial eruption, children may have Nikolsky's sign of epidermal exfoliation upon tangential

pressure. A child's initial complaint may be of a 'tummy ache' from tender skin overlying the abdomen.³³ SSSS initially becomes evident as abrupt, faint, erythematous, tender patches. Over a period of hours, the patches become well demarcated and coalesce into a confluent scarlatiniform erythema. Fragile bullae develop within the erythematous areas that can extend to large sheets of epidermal detachment, beginning on the central face, axillae, groin and neck, leaving swaths of moist, red surface that appear scalded. The denuded skin is a source for fluid loss, dehydration and temperature dysregulation. The denuded skin may also serve as a nidus for secondary infection.^{1,18,34} Within 24 h of exfoliation, the areas dry with a thin, shiny crust and fissures in perioral or periorbital skin.³⁵ The child will have a second period of desquamation during the following 10 days. Within 14 days the skin heals without scarring.³⁵

Clinical features in adults

It was not until 1972 that SSSS was described in an adult.¹⁴ A German study of its incidence revealed that 36% of SSSS cases were in adults.¹ Unlike paediatric patients with SSSS, adults may present differently; a majority of adults grow *S. aureus* from blood cultures (Table 1).^{29,31} In addition, as opposed to paediatric patients who are usually in otherwise good health when they develop SSSS, virtually all adults with SSSS were immunocompromised, with chronic renal disease, HIV infection, graft-versus-host disease, malignant neoplasms, chemotherapy, intravenous drug abuse or diabetes mellitus.^{14,28,36–49} Similar to paediatric patients, adults with SSSS demonstrate a fever, and oedematous erythema of the eyelids and nostrils. Generalized erythema, bullae formation and desquamation of the skin may also occur, but the mucosal surfaces are usually not involved. Possibly as a result of underlying morbidities, adults with SSSS have a mortality rate of 40–63%.^{1,29}

Diagnosis

A vesiculobullous disorder with a positive Nikolsky's sign and a scalded skin appearance (Fig. 1), SSSS may initially resemble other blistering disorders, including toxic epidermal necrolysis (TEN), a life threatening immunological reaction to a drug or infection⁵⁰ (Table 2). However, SSSS can be differentiated from TEN by lack of mucous membrane involvement as well as by more superficial epidermal peeling, which is in contrast to the

Table 1 Staphylococcal scalded skin syndrome: children vs. adults

	Children	Adults
Underlying illness	None	Immunosuppressed or renal disease
Source of infection	Difficult to determine	Pneumonia, osteomyelitis, septic arthritis
Blood cultures	Usually negative	Usually positive
Mortality	2.6–11%	40–63%



Figure 1 Staphylococcal scalded skin syndrome. Characteristic desquamation in gravely ill woman.

Table 2 Findings in blistering disorders

Disease	Morphology	Histological finding	Medication cause
SSSS	Bullae	Intraepidermal cleavage	No
SJS/TEN	Bullae	Subepidermal cleavage	Yes
DRESS	Morbilliform	Perivascular lymphocytes, eosinophils	Yes
Enterovirus	Vesicles/bullae	Subepidermal cleavage	No*
STSS	Bullae	Substratum granulosum cleavage	No

*Probably a variant of SJS/TEN.

DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens–Johnson Syndrome; SSSS, Staphylococcal scalded skin syndrome; STSS, staphylococcal toxic-shock syndrome; TEN, toxic epidermal necrolysis.

full thickness denudation found in TEN.⁵¹ A histological examination can also rapidly differentiate between SSSS and TEN. Even a sample of the roof of an intact bulla taken to a laboratory in saline-moistened gauze can be processed for frozen section to histologically demonstrate subcorneal cleavage,⁵² but we recommend a skin biopsy.

Infection with human enteroviruses, such as coxsackie virus, echovirus and enterovirus type 71, can produce blistering that may be confused with other disorders, including SSSS, and Stevens–Johnson syndrome/toxic epidermal necrolysis. Unlike SSSS, which has subcorneal separation within the epidermis, these disorders, such as in hand-foot-mouth disease, may produce epidermal necrosis and keratinocytes dyskeratosis, resulting in epidermal–dermal separation and mucocutaneous blistering. Although similar histopathologically to Stevens–Johnson, enterovirus-induced blisters do not involve the oral mucosa, and

unlike TEN, the skin involvement is limited to less than 10% body surface area.⁵³

SSSS is not a result of medication. However, SSSS may be confused with drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), also referred to as the drug-induced hypersensitivity syndrome. This medication-induced reaction is first evident weeks later than TEN.⁵⁴ Characteristically associated with anticonvulsants and sulphonamides, this potentially life-threatening syndrome begins suddenly with fever followed by an erythematous eruptions on the face, trunk and extremities and may progress to bullae formation. Evaluation of serum IgG to HHV-6 may demonstrate elevated titres in patients with DRESS. A biopsy specimen in DRESS will show a prominent perivascular lymphocytic infiltrate in the papillary dermis, along with eosinophils and atypical lymphocytes.⁵⁵

Staphylococcal scalded skin syndrome can also be distinguished from other *S. aureus*-linked conditions such as staphylococcal toxic-shock syndrome (STSS), which also is associated with exfoliatins. The mild forms of these two staphylococcal diseases may resemble each other with fever, hypotension and a desquamating rash.^{18,56} Additional skin changes in STSS include petechiae and desquamation of the palms and soles. In both conditions, cultured bullae fluid is generally sterile.³⁵ However, SSSS has bullae that exfoliate and have a positive Nikolsky's sign.¹⁸ Patients with SSSS are also more likely to have facial and skin fold involvement than STSS.⁵⁶

Mild forms of *S. aureus* toxin-mediated infection are evident in children. In SSSS, *S. aureus* is not present in the skin lesions, but rather is confined to the site of infection, primarily the nasopharynx.¹⁸ Blood cultures do not typically help in diagnosis of a child with SSSS, as they are usually negative.³¹ However, in adults blood cultures are generally positive and be a clue in diagnosis.

Dermatopathology

A skin biopsy specimen may establish the diagnosis of SSSS, showing superficial intraepidermal cleavage under the stratum corneum. Both TEN and SSSS lack inflammation, but SSSS does not have the necrotic keratinocytes characteristic of TEN (Fig. 2).³⁵ Presence of only a stratum corneum with a single epidermal cell layer reflects that the process producing SSSS is toxin-mediated.³⁵ Histology in SSSS is a result of staphylococcus exfoliative toxin cleaving a specific peptide bond on Dg1. Because of this precise mechanism, histology of SSSS is also consistent with other conditions of Dg1 cleavage, specifically pemphigus foliaceus and bullous impetigo. In fact, SSSS had been called 'pemphigus neonatorum'.⁵⁷

Prognosis

If treatment is begun promptly, the mortality rate can be minimized in children. Therapy includes supportive measures such as nasogastric feeding, intravenous fluids, and intravenous

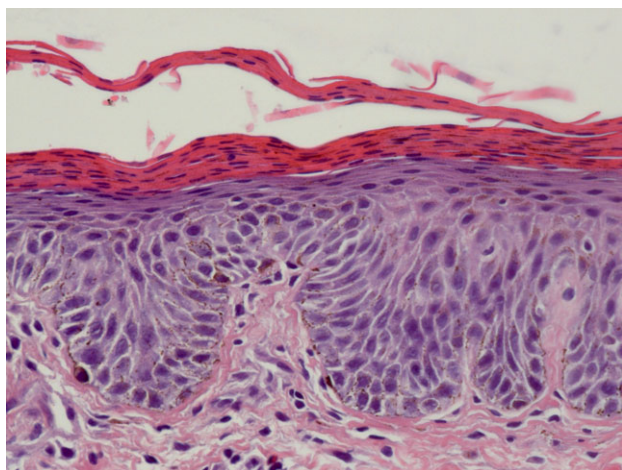


Figure 2 Staphylococcal scalded skin syndrome. Skin histopathology revealing intraepidermal cleavage through the stratum granulosum with little dermal inflammation. (Haematoxylin and eosin, original magnification $\times 400$).

antibiotics.³³ The denuded skin will reepithelialize within 6–12 days without scarring. In adults the prognosis is much worse, as it is generally seen in individuals with serious comorbidities, accounting for up to 63% mortality even with initiation of appropriate antibiotics.^{26,29}

Management

Treatment requires a combined approach, often best accomplished in an intensive care or burn unit (Table 3). Although SSSS will continue to progress for another 24–48 h after onset until circulating exotoxin has been neutralized by antibodies or excreted via the kidneys, it is important to start antibiotics as early as possible.²⁷ Penicillinase-resistant penicillins are recommended, as they treat the methicillin-sensitive *S. aureus* infection seen in most patients.²⁹ An example dose for children is flucloxacillin intravenous 50–100 mg/Kg/day and for adults 500–1000 mg per day, both divided into four portions.³³ If the

patient has a penicillin allergy, clarithromycin or cefuroxime may be used. Debate exists whether antibiotics delivered intravenously have superior efficacy than oral administration.⁵⁸ If a patient is not improving, it is necessary to consider ET produced by methicillin-resistant *S. aureus* and switch to vancomycin.⁵⁸

Because 91% of adults older than 40 years have antibodies against ETA, systemically unwell children may receive a dose of fresh frozen plasma (FFP) (10 mL/kg) to neutralize exotoxin antibodies.^{59,60} This therapy has been successfully used in a paediatric case series, but no large trials of FFP in SSSS have been performed in children or adults. For children who have not benefited from FFP, a 5-day course of intravenous immunoglobulin (IVIG) (0.4 g/kg per day) can be tried to neutralize the exotoxins.^{27,61} This approach should be successful in both affected children and adults, but has only been reported to work in children.^{27,61} However, a recent retrospective study found those treated with IVIG for SSSS had longer hospitalizations than those not receiving IVIG.¹⁵

Additional investigation should be made into the focus of staphylococcus infection if it remains unknown. Cultures should be performed on possible sites, such as blood, wounds, ocular exudates and nasopharynx. In adults, the primary infection site is likely an obvious clinical infection such as pneumonia, osteomyelitis or septic arthritis. In children, the primary infection site is usually a mild upper respiratory tract infection.²⁷

Fluids

Similar to an extensive burn, patients with SSSS must receive intravenous fluids to compensate for fluid loss and prevent hypovolemia. In paediatric patients fresh frozen plasma given as a bolus of 10% of a child's circulating volume (70 mL/Kg) may be employed, followed by maintenance fluid of dextrose 4% in saline 0.18% at a weight-dependant rate, such as by the '4-2-1' rule.⁶² Despite a significant risk of hypovolemia from fluid loss, a risk of hyponatremia exists, likely from inappropriate vasopressin release coupled with excess volumes of intravenous fluids given.²⁷ Due to a risk of hyponatremia after the initial boluses, 0.45% saline with 5% dextrose has been recommended as

Table 3 Management of Staphylococcal scalded skin syndrome

Clinical scenario	Treatment	Dose	Level of evidence
All cases of SSSS	Systemic penicillinase-resistant antibiotic	flucloxacillin 50–100 mg/Kg/day divided in four doses	IV
Tender skin	Analgesia	Acetaminophen and fentanyl (1–4 μ g/kg/h)	IV
Sloughing skin	Dressings, and placement in a specialized unit, burn unit, or ICU		IV
Sloughing skin	IV Fluids	Bolus + Maintenance: 0.45% saline with 5% dextrose as maintenance fluid	IV

Level of evidence: IA evidence includes evidence from meta-analysis of randomized controlled trials; IB evidence includes evidence from at least 1 randomized controlled trial; IIA evidence includes evidence from at least 1 controlled study without randomization; IIB evidence includes evidence from at least 1 other type of experimental study; III evidence includes evidence from non-experimental descriptive studies such as comparative studies, correlations studies and case-control studies; IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

maintenance fluid. The child should receive a central venous access line for blood sampling of urea, electrolytes and blood gases every 8–12 h, and a urinary catheter to measure urine output.

Dressings

To avoid secondary infection and facilitate recovery, dressings must be placed over denuded skin.³³ The denuded areas should be dressed with a soft silicone primary wound dressing (such as Mepitel®, Norcross, GA, USA) covered by saline-soaked gauze.³³ In patients with large surface area to volume ratios of denuded skin, one should avoid betadine and silver sulfadiazine due to risk of toxic systemic absorption of iodine and silver respectively.⁶³ If skin loss is small, sterile dressings of silver sulphadiazine cream and paraffin-impregnated gauze covered by gauze and cotton tissue can be used for the trunk. As areas heal, hydrocolloid dressings may be applied.²⁷

Analgesia with acetaminophen and opiates, such as fentanyl, may be administered as needed. Non-steroidal anti-inflammatories should be avoided, as they are excreted by the kidneys and increase the risk of bleeding.³³

In paediatric patients, sedation with midazolam (50–100 µg/kg/h) may be of benefit. For pruritus in children, medications may be utilized as needed. In children nasogastric or naso-jejunal tube may be placed to provide enteral nutrition.

In children and adults bedding should allow for comfortable immobility. Forced-air warming blankets should replace heavy blankets and provide a core temperature of 37–38°C. Physiotherapy should be performed to encourage joint mobility.²⁷

Conclusion

With a rise in SSSS among paediatric patients and a rise in SSSS risk factors among adults, clinician awareness of SSSS is important in early diagnosis and treatment.^{15–17,64} Treatment should be geared at antimicrobial administration in both affected children and adults. In such cases that an affected individual does not improve with antibiotic therapy, the addition of exotoxin neutralizing agents, such as FFP and IVIG, can be tried, although double-blinded, randomized, placebo trials have not been performed. As a result of epidermal volume loss, fluid management is critical in treatment of SSSS. Electrolytes should be checked regularly and special attention paid to hyponatremia resulting from nosocomial volume overload. Equally important in management of patients with SSSS is prevention of secondary infection through denuded skin. Wound care, analgesia, body temperature management and physiotherapy should be instituted to promote healing and minimize further morbidity. In children, it remains unknown why SSSS develops but the mortality rate remains low. Blood cultures will usually be negative with denuded skin healing within 2 weeks without scarring. In affected adults it is apparent that immunosuppression places increased risk for SSSS. It remains unclear whether development

of SSSS expedites mortality in adults or is a clinical finding in those who already have a high risk of death. Further studies on both cause and management of children and adults with SSSS are desirable to minimize morbidity and mortality.

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