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Staphylococcal Scalded Skin Syndrome
Diagnosis and Management

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Contents

Abstract

Staphylococcal scalded skin syndrome (SSSS) is a common disorder that is usually seen in infants and children and rarely seen in adults. SSSS usually presents with a prodrome of sore throat or conjunctivitis. Extremely tender flaccid bullae, which are Nikolsky sign–positive, develop within 48 hours and commonly affect the flexures; occasionally, large areas of the skin may be involved. The bullae enlarge and rupture easily to reveal a moist erythematous base, which gives rise to the scalded appearance.

SSSS in adults is a rare disorder, though there are now over 50 documented cases. Usually SSSS occurs in predisposed individuals, but not all adults have an underlying illness. Whereas mortality in childhood SSSS is approximately 4%, the mortality rate in adults is reported to be greater than 60%.

SSSS is caused by an infection with a particular strain of *Staphylococcus aureus*, which leads to blistering of the upper layer of the skin, by the release of a circulating exotoxin. It has recently been demonstrated that the exfoliative exotoxin responsible for SSSS leads to the cleavage of desmoglein 1 complex, an important desmosomal protein. The same toxins that are responsible for causing SSSS also cause bullous impetigo. There appears to be a relationship between the disease extent, the amount of toxin produced and whether the toxin is released locally or systemically. As a result there is likely to be a spectrum of disease and there are likely to be a number of milder cases of adult SSSS that go undiagnosed.

Social improvements and hygiene have led to a dramatic fall in the number of cases of SSSS. Treatment is usually straightforward, when there is no coexistent morbidity and the presentation is mild, but can be demanding if the patient is particularly ill. SSSS is still associated with mortality, particularly when it occurs in adults.

1. Historical Perspective

Staphylococcal scalded skin syndrome (SSSS) is a disorder that is usually seen in infants and children and rarely seen in adults. It is caused by an infection with a particular strain of *Staphylococcus aureus*, which leads to blistering of the upper layer of the skin, by the release of a circulating exotoxin.

Baron Gotfried Ritter von Rittershain[1] first described the disease in the newborn in 1878. Over a 10-year period, the Baron observed 297 cases in a Prague hospital. He called the disease 'dermatitis exfolitiva neonatorum', but it was later referred to as 'Ritter's disease'.

After the retirement of Baron Ritter von Rittershain, observations of the disease lessened. This may have been because of improvements in hygiene at that time. In 1956, Lyell[2] coined the term 'toxic epidermal necrolysis' (TEN) and described four cases. However, in that same publication Lyell erroneously grouped TEN and SSSS together.[2] This led to confusion and a

number of papers on SSSS erroneously described as TEN were published.[3-7] In 1970, Melish and Glasgow[8] discovered the etiological agent for SSSS to be *S. aureus* and reproduced the skin changes of SSSS using *S. aureus*–cultured supernatant in a neonatal mouse model. They called this disease entity SSSS.[8] These findings were reproduced by a number of other studies, adding to the growing strength of evidence to separate the two disorders, TEN and SSSS.[9-11] Later Lyell[12] accepted his error and published a paper on the historical aspects of SSSS.

The first adult case of SSSS was described in 1972.[13] SSSS in adults is a rare disorder, although there are now over 50 documented cases. Usually SSSS occurs in predisposed individuals but not all adults have an underlying illness.[14]

Amagai et al.[15] demonstrated that the exfoliative exotoxin responsible for SSSS leads to the cleavage of desmoglein 1 (DG1), an important desmosomal protein. The same toxins that are responsible for causing SSSS also cause bullous impetigo.[16,17] There appears to be a relationship between the disease extent, the amount of toxin produced and whether the toxin is released locally or systemically.[16,17]

2. Diagnostic Features

The diagnosis of SSSS is based on clinical, histological and microbiological findings:[18]

- a clinical pattern of tenderness, erythema, desquamation or bullae formation
- histopathological evidence of intraepidermal cleavage through the stratum granulosum
- isolation of an exfoliative exotoxin A (ETA) and/or exfoliative exotoxin B (ETB) producing *S. aureus*
- the absence of pemphigus foliaceous by direct and indirect immunofluorescence.

3. Clinical Features

SSSS usually presents in children under the age of 5 years[19] with a prodrome of sore throat or conjunctivitis. The conjunctivitis can be severe, with both periorbital edema and purulent discharge, frequently yielding the causative *S. aureus* on culture. Within 48 hours the patient develops fever, malaise and extremely tender erythematous patches on the face, neck, axilla and perineum (figure 1). Flaccid bullae develop within the erythematous areas and the Nikolsky sign is positive.[20] The bullae commonly affect the flexures and occasionally large areas of the skin may be affected. Bullae enlarge and rupture easily to reveal a moist erythematous base, which gives rise to the scalded appearance. Healing occurs without scarring.

SSSS tends only to occur once and, if treated adequately with antibiotics, usually resolves within days. There is one report of a 50-year-old woman with epilepsy and cerebellar ataxia who developed recurrent episodes of SSSS over 2 years.[21] In patients with extensive blistering, as typically occurs in adults, management may be complicated by hypothermia, hypotension, electrolyte disturbance, neutropenia, respiratory distress and/or secondary infection. In adults there is often a definable source of sepsis that may further complicate the management.

A localized variant of the disorder has been described on a number of occasions.[22-24] In one report a 72-year-old woman developed exfoliation limited to her left flank,[23] and in another case a 54-year-old man had erosions limited to his right arm and upper chest.[22] In contrast, bullous impetigo is caused by a direct innoculum of *S. aureus*, resulting in only localized release of *S. aureus* exfoliative exotoxin. The surrounding skin in bullous impetigo is inflamed, and the associated serous exudates and the resultant golden-yellow crust is rich in bacteria. The host response in bullous impetigo results in an acute localized inflammatory response (figure 2).

The diagnosis of SSSS is based on clinical, histological features and SSSS can be distinguished from TEN (figure 3) by these features, as well as cause and natural course of the disease.[16,25] In contrast to SSSS, TEN tends to occur in isolated cases in patients over 20 years and there is usually a clear history of drug ingestion prior to presentation. The lesions in TEN are also tender, but start on acral sites and involve mucous membranes (figure 3). While in affected skin the Nikolsky sign is positive in both conditions, in SSSS it is often demonstrated in unaffected skin also. TEN is clearly distinguishable from SSSS by conventional histology, which in TEN shows full thickness epidermal necrosis. To date, there is no curative treatment for TEN. SSSS, in contrast, is caused by an exfoliative exotoxin-producing *S. aureus*, and usually responds to appropriate antibiotics. Making the correct diagnosis is, therefore, fundamental to successful management of either condition. The natural course of TEN is between 1–3 weeks and is associated with up to 50% mortality.[16]

4. Histology

Histopathology from the edge of an erosion reveals a subcorneal split along the granular cell layer resulting from intraepidermal acantholysis (figure 1c). There is little to no dermal inflammatory cell infiltrate and no cell necrosis.[26] Electron microscopy confirms widening of the intracellular spaces along the granular cell layer, with loss of desmosomes.[27]

The histopathological features of the split are similar to that found in bullous impetigo. However, in bullous impetigo there is

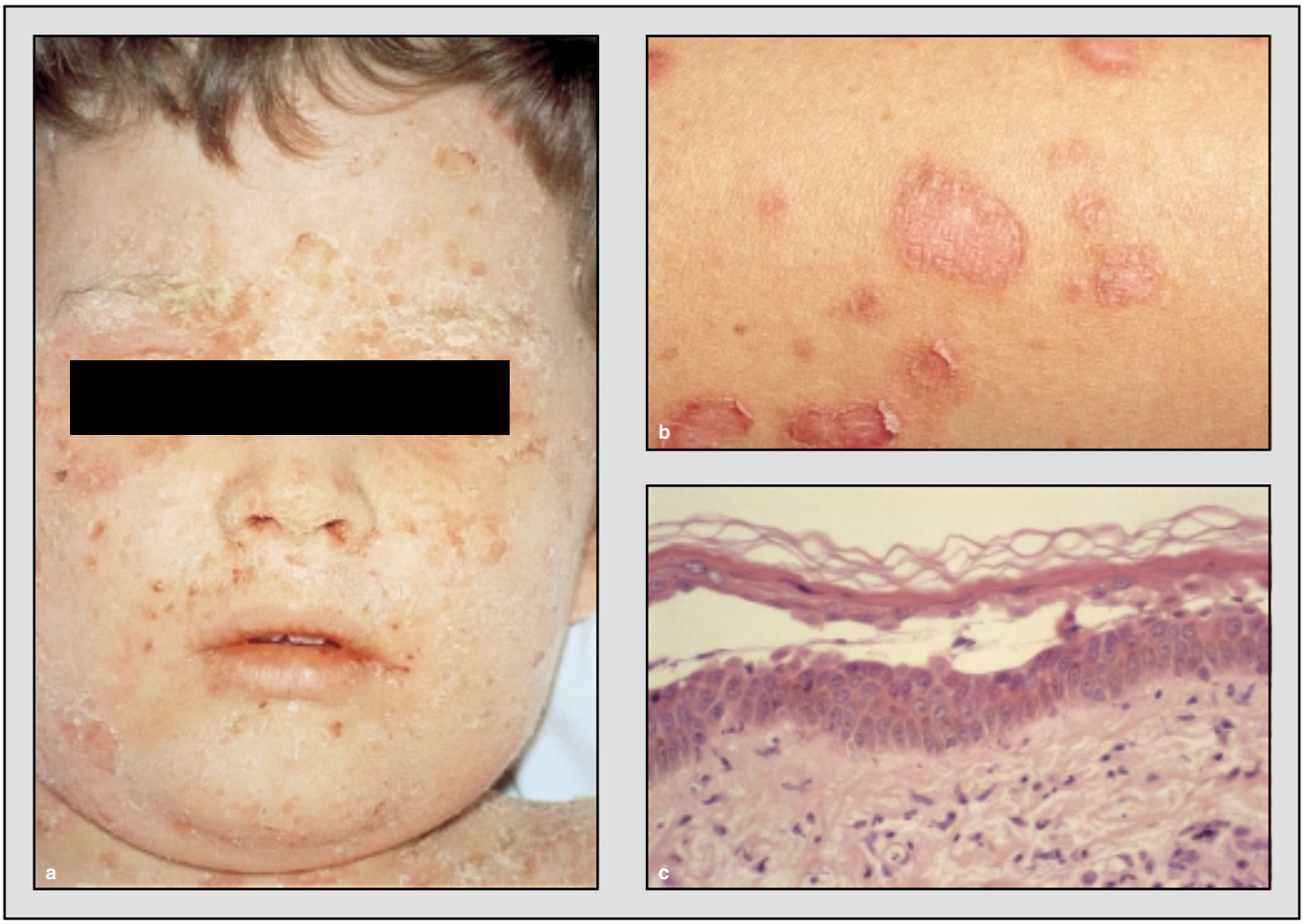

Fig. 1. Staphylococcal scalded skin syndrome (SSSS) typically affects infants and children under 5 years old. It usually follows a prodrome of a sore throat or conjunctivitis. **(a)** SSSS typically causes blistering affecting the face, neck, axilla and perineum, although it may be more widespread. The appearance of an unhappy and unwell child as seen in (**a**) is common. (**b**) Blistering is superficial and is often seen as erosions. (**c**) The histology from the edge of the blister reveals a sub-corneal blister resulting from acantholysis associated with little or no inflammatory cell infiltrate.

a pronounced inflammatory cell infiltrate consisting mostly of neutrophils[22] (figure 2b).

Pemphigus foliaceous (figure 4) and subcorneal immunoglobulin A pemphigus also have a split along the granular cell layer. Both conditions are associated with a dermal inflammatory cell infiltrate and direct immunofluorescence is usually positive, helping to distinguish them from SSSS.[28]

The histological features of SSSS are distinct from TEN. TEN is characterized by full thickness epidermal cell necrosis and basal layer vacuolar degeneration, which may lead to a dermoepidermal split. Occasional mononuclear cells within the epidermis are associated with dyskeratotic keratinocytes (satellite necrosis)[26,29] [figure 3d]. The thickness of the overlying epidermal roof will therefore allow quick and easy histological differentiation between the disorders.[26]

5. Microbiology

SSSS occurs in patients with an occult or overt infection or colonization with exfoliative exotoxin–secreting *S. aureus*. Most strains of *S. aureus* isolated from such patients belong to phage group II and the most common subtypes are 3A, 3B, 3C, 55 and 71.[30,31] Phage group II strains are characterized by their ability to make serum agar opaque, produce a negative egg-yolk reaction and cause a zone of inhibition when cultured alongside *Corynebacterium diphtheriae*.[32] Infrequently, SSSS is caused by group

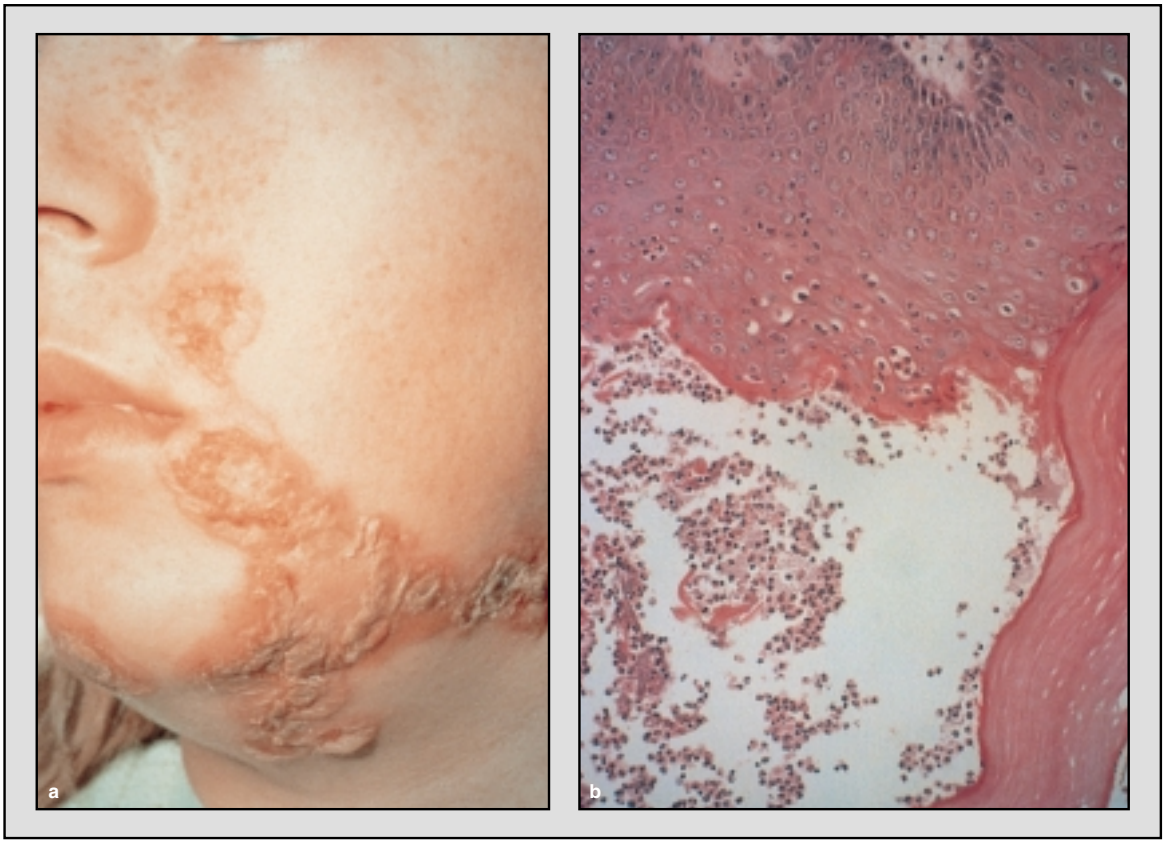

Fig. 2. (**a**) Bullous impetigo, in contrast to staphylococcal scalded skin syndrome, is a localized eruption associated with a marked inflammation. Characteristically it is highly contagious and particularly common among children. (**b**) The histological findings of a subcorneal blister associated with a neutrophil-rich infiltrate and Gram-positive organisms are typical.

I and III *S. aureus*.[31] The strains of *S. aureus* responsible for SSSS secrete exfoliative exotoxin. Exotoxin secretion occurs during the bacterial logarithmic growth phase.[33] The same exotoxins are responsible for the localized blistering seen in bullous impetigo, which is caused by a direct innoculum.[33-35] In contrast, SSSS results from systemic circulating exotoxin, leading to a generalized eruption.[36] There have been a number of cases of localized SSSS reported,[17] suggesting that there is a spectrum of disease presentation based on the extent of skin exposure to the toxin.

So far two exfoliative exotoxins have been identified, ETA and ETB.[37,38] ETA is the most commonly secreted toxin; it is a heat-stable protein and is encoded on the bacterial chromosome, produced by 89% of isolates.[39] ETB is a plasmid-derived heat-labile protein, which is produced by 4% of isolates. In the remaining 7% both ETA and ETB are co-secreted.[40] Over 80% of strains that produce exfoliative exotoxins belong to phage group II, the majority of which produce ETA.[31] There are geographic differences in the incidence of the different strains of *S. aureus*. In Japan, *S. aureus* appears to secrete ETB rather than ETA, furthermore the prevalence of ETB-secreting *S. aureus* appears to be increasing.[41-43]

A number of methods are now available to determine the presence of *S. aureus* that produce exfoliative exotoxins. In most clinical scenarios, phage typing of *S. aureus* is sufficient to aid a diagnosis of SSSS, particularly in Europe and the USA where phage type II is the most common cause. However, for detection of the exfoliative exotoxin, the newborn mouse assay is still considered the reference test.[8] There are now a number of immunological methods for accurate characterization of the exfoliative exotoxins. These tests include double immunodiffusion, slide latex hemagglutination, radio-immunologic assay, enzyme-linked immunosorbent assay and DNA hybridization.[40,44-46] Molecular biology methods using specific polymerase chain reaction-generated probes to the ETA and ETB genes provide even greater accuracy.[45]

In children, transmission of exfoliative toxin–producing *S. aureus* appears to be through asymptomatic carriers and hence it is important to screen for potential carriers.[47] Asymptomatic carriage of *S. aureus* by staff working in a neonatal baby unit has led to outbreaks of SSSS.[43,48,49] The resultant infection in children is not usually clinically overt, except in cases when conjunctivitis is present; the blistered skin is culture-negative. In the reported cases of adults with SSSS the source and site of *S. aureus* infection is varied, including cardiac catheterization,[50,51] abscesses,[13,52,53] septic arthritis,[40,54] infected arteriovenous shunt[55,56] and parenteral injection,[28,51] although the source of infection was not apparent in all cases. *S. aureus* can be isolated from the blood of most adults with SSSS, but from less than 3% of childhood cases.[40]

Approximately 5% of all *S. aureus* isolates cultured in a hospital laboratory secrete exfoliative exotoxins.[57] Colonization with exfoliative exotoxin–producing *S. aureus* is greater in neonates, up to 3% of whom are unaffected carriers.[57] In a study of pregnant women attending an antenatal clinic, 1% were found to be asymptomatic carriers from nose, axilla and perineal swabbing.[58] Despite such high colonization rates, SSSS is uncommon.

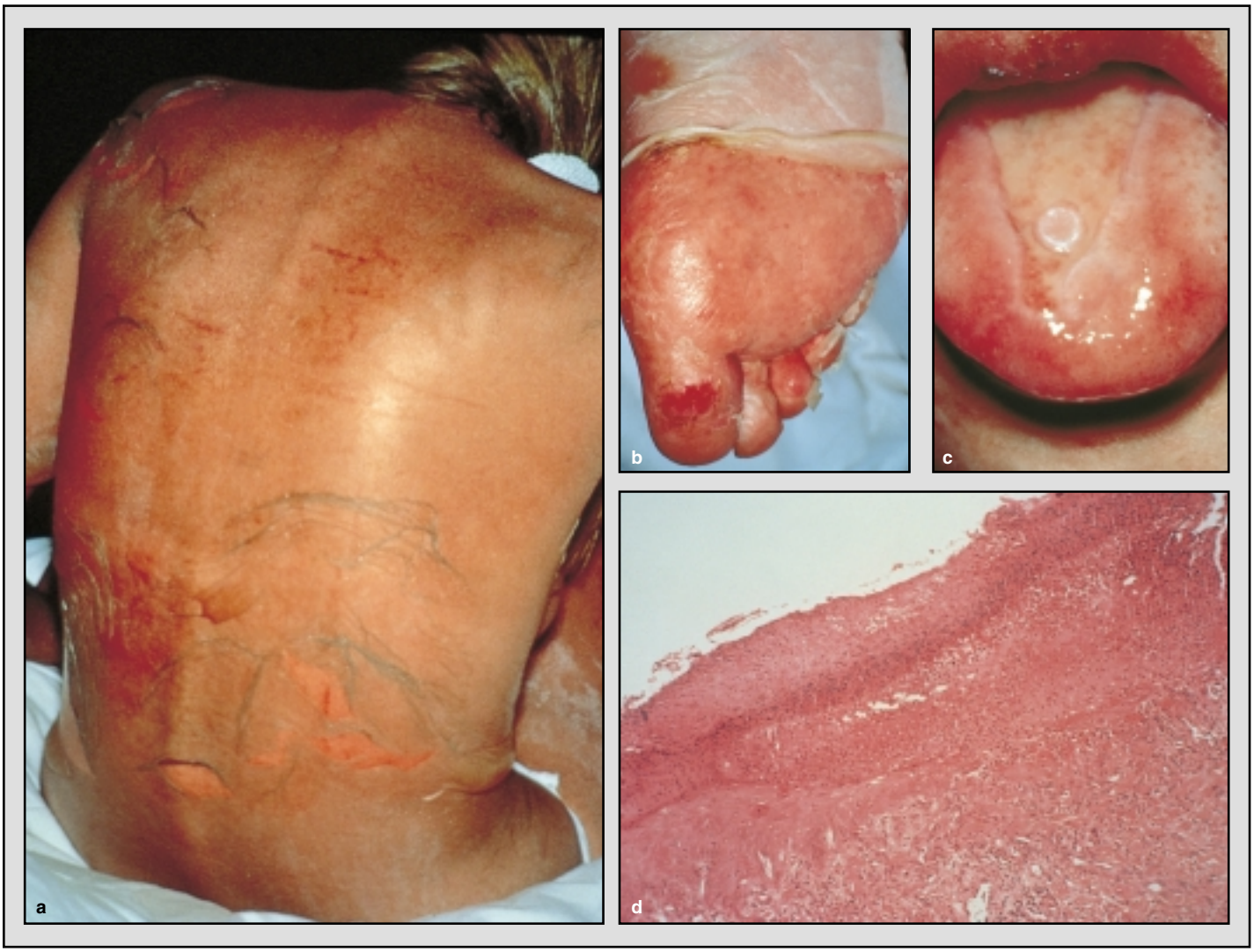

Fig. 3. Toxic epidermal necrolysis, in contrast to staphylococcal scalded skin syndrome, is usually attributed to an adverse drug reaction. Toxic epidermal necrosis classically causes epidermal and mucous membrane cell necrosis (**a**) and (**b**), resulting in painful widespread skin full thickness erosions; (**c**) also affecting mucous membranes such as the lips and tongue. (**d**) Histology characteristically shows a marked dermal lymphocytic infiltrate associated with full thickness epidermal necrosis.

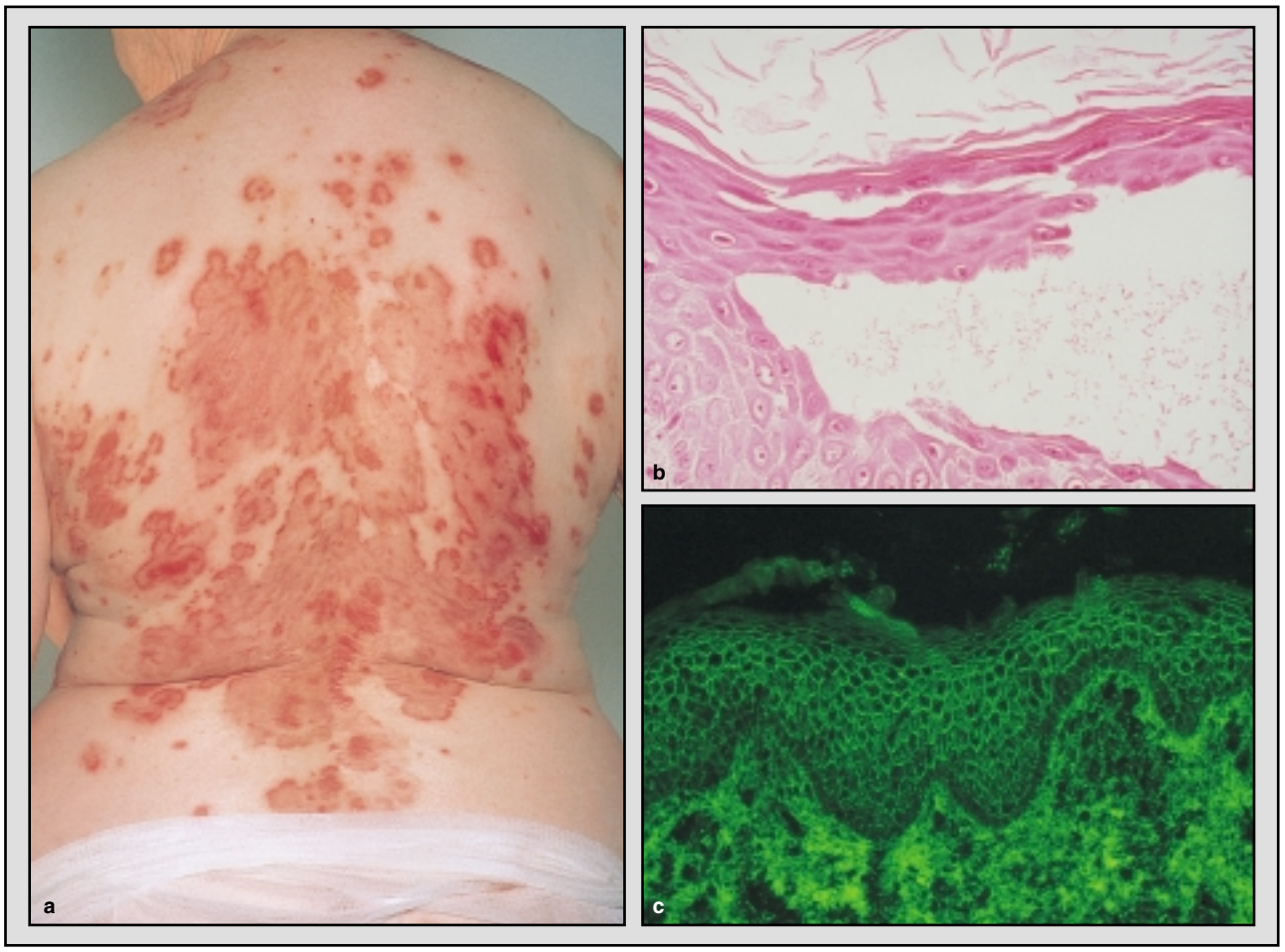

Fig. 4. (**a**) Pemphigus foliaceous is an immunoglobulin G (IgG) autoantibody–mediated autoimmune disorder targeting desmoglein 1 proteins and, like staphylococcal scalded skin syndrome, causes widespread superficial blisters and erosions. (**b**) Histology reveals a subcorneal blister that is associated with minimal inflammatory cell response, but positive direct and indirect immunofluorescence. (**c**) Direct immunofluorescence is characterized by a plasma membrane–bound IgG affecting the superficial keratinocytes.

Occasionally, other *S. aureus* toxins may cause an SSSS–like eruption.[59-61] In these situations, management of the disorder may need to more aggressive, particularly in toxic shock syndrome.[59]

6. Pathogenesis

There have been recent advances in understanding how exfoliative exotoxin causes blisters and how to identify those at greatest risk of developing SSSS. The toxin has exquisite specificity in causing loss of desmosome-mediated cell adhesion within the superficial epidermis only.[60,62] The target antigen has recently been identified.[15]

Initial experiments showed that the blistering seen in SSSS could be reproduced in mice by subcutaneous injection with the supernatant obtained from culture of *S. aureus* from patients with SSSS. This lead to erythema and epidermal fragility within a few hours.[63] Later the toxin responsible for SSSS was isolated and subsequent experiments showed that if given by intraperitoneal injection to newborn mice, blistering occurred in a dose-dependent manner.[13,64] Mice older than 5 days were not susceptible to blistering,[63] but the level of exfoliative exotoxin in the serum was close to the lower limit for detection.[65,66] More recently the nucleotide sequences of both ETA and ETB have been established,[67-69] their respective genes have been sequenced[70,71] and the ETA gene has been cloned in *Escherichia coli*.[72]

Immunohistochemical studies showed that ETA binds to fillagrin in the keratohyalin granules of the granular layer cells.[73,74] As fillagrin is the intracellular anchor for desmo-

somes, this led to the hypothesis that epidermal splitting resulted from the rupture of desmosomes by the proteolytic activity of the toxin.[16,75-77] Incubation of ETA with neonatal mouse epidermis or neonatal mouse epidermal extract results in the induction of caseinolytic activity in the supernatant.[78,79] Further support for the hypothesis followed the discovery that there are structural similarities between the staphylococcal V8 protease, particularly in the serine-aspartic acid-histadine catalytic triad that forms the active site, and trypsin-like serine proteases.[16] Replacement of any of these three central amino acids resulted in complete loss of their biological activity when the exfoliative exotoxin was injected into newborn mice.[76,77,79] Moreover, computer modeling[79] and crystallography[75] of the three-dimensional structure revealed a high degree of similarity with known glutamate-specific trypsin-like serine proteases. Though *in vitro* and *in vivo* studies using protease inhibitors failed to prevent epidermolysis,[16,75] most authors still believe that these exotoxins are proteases.[37,80]

DG1 has been suspected to be the target antigen for the exfoliative exotoxins because of the histological and clinical similarities between SSSS and pemphigus foliaceous.[37] DG1 is expressed throughout the epidermis, but in the lower epidermis desmoglein 3 (DG3) is co-expressed and prevents blister formation at this level.[81] In a series of experiments Amagai et al.[15] showed DG1 to be the target antigen for ETA. Initially by injecting ETA into neonatal skin, then performing direct immunofluorescence on skin epidermis using antibodies that targeted DG1 and DG3, they saw reduced, disrupted and cytoplasmic staining instead of membrane staining of DG1. The DG3 staining pattern was normal. HaCaT keratinocyte cells were then transfected with complementary DNA (cDNA) encoding mouse DG1 and also DG3 containing a FLAG octapeptide epitope on its carboxyl termini. These transfected cells were then incubated with ETA. Western blot analysis with antibodies against FLAG peptide revealed degradation of DG1, but not the closely related DG3. Neonatal mice were then injected with ETA. Western blot analysis was used for DG1, DG3 and epidermal cadherins on the skin extracts of superficial blisters and showed degradation of DG1, revealing a cleaved fragment of 113kDa; the usual size of DG1 is 160kDa. Cleavage most likely occurred at a glutamic acid residue in DG1, as suspected previously,[75] and a cleavage site was identified in the protein sequence that was consistent with the resultant cleaved product. Furthermore, the group went on to demonstrate dose-dependent cleavage of the extracellular domain of mouse and human DG1. However, it still remains to be confirmed exactly how ETA binding to DG1 leads to its proteolysis.

Another theory proposed is that the two exfoliative toxins may act as superantigens;[82] however, the lack of inflammatory infiltrate on histology does not support this view.

Despite the high prevalence of ETA and ETB exotoxin–producing *S. aureus*, there appear to be a number of other factors necessary before SSSS occurs. Healthy adults rarely develop SSSS; there are only four reported cases.[16,40,50] One explanation for this rarity is the formation of antibodies against ETA and ETB, which may compromise the effect of these toxins. Indeed 91% of adults have antibodies to ETA. Antibodies to ETA could be detected in 88% of cord samples, reflecting maternal antibody transfer status. However, antibody levels were detected in only 30% of babies aged 3 months to 2 years, but then rose steadily so that at 2 to 5 years, 42% had ETA antibodies and in adults over the age of 40 years 91% had antibodies.[83] In patients with SSSS, antibodies were initially absent, but then appeared in the convalescent sera.[83-85] In contrast, patients with bullous impetigo had circulating antibodies throughout the illness.[83]

7. Predisposing Factors

Other factors, usually present in adults, are also important in the development of SSSS. These include excessive exotoxin burden, increased *S. aureus* carriage rate and increased susceptibility to the toxin.

Renal failure is the most common underlying cofactor in adults developing SSSS.[13,52,55,56,86-89] An experiment on nude mice has revealed that the exotoxin is excreted through the kidney, and impairing renal excretion of the exotoxin aggravates the disease.[90] A study of patients with renal failure undergoing dialysis showed that the carriage rate of *S. aureus* is 3-fold greater than would be expected.[91] Recently, SSSS has been described in an individual taking a nonsteroidal anti-inflammatory drug: these drugs promote *S. aureus* growth and decrease renal clearance of the toxin.[83]

The second most common reason why adults may develop SSSS is overwhelming *S. aureus* burden, usually resulting in septicemia.[51,92,93] Those at greatest risk are patients with immunosuppression. A study in animals[34] has demonstrated that immunosuppression allows for a greater proliferation of *S. aureus* and therefore exotoxin production. This may be a result of immunosuppressive drugs,[94,95] poor cell-mediated immunity,[22] HIV,[56,96,97] chronic alcohol abuse,[23,53,86,98] heroin addiction,[47] malignancy[26,87,94,99,100] and possibly also diabetes.[21] One patient with cachexia secondary to a benign esophageal stricture, who developed severe sepsis and then SSSS, has also been described.[51]

SSSS is rare in adults, probably because of the formation of antibodies and the presence of adequately functioning kidneys that are able to effectively excrete the exotoxin. Although there have been a few cases in which there has been no identifiable predisposing factor,[14,40,50] serum antibodies against exfoliative exotoxins were not measured in these patients.

8. Management

Prompt diagnosis and early treatment with parenteral antistaphylococcal antibiotics, such as flucloxacillin is essential.[101,102] All strains of *S. aureus* isolated in reported cases have been penicillin-resistant,[8] but are usually sensitive to semisynthetic penicillins.[103] Although methicillin-resistant strains of *S. aureus* associated with SSSS have occasionally been described,[59,104] most cases are a result of phage group II *S. aureus*, in which multi-resistance is rarely seen.[29]

Blisters should be left intact. Eroded areas are best covered with white petrolatum–impregnated gauze, which helps reduce further trauma to the skin. A topical antibiotic or antiseptic eye ointment is helpful to manage the conjunctivitis.

In cases with severe skin loss, consideration needs to be given to:

- the best location for the patient (consider intensive care unit)
- mattress requirement
- pain management
- temperature regulation
- fluid management
- nutritional care
- infection risk assessment and management
- skin care.

Patients are best managed in isolation for the early period, so that the infection of others can be prevented. Pressure-relieving mattresses that allow the patient to be comfortable will reduce the possibility of pressure sores developing. Pain because of skin tenderness is a major cause of morbidity and adequate analgesia should be given, which may necessitate opioids. Thermal dysregulation can occur because of underlying infection, severity of illness and peripheral vasodilatation. The core temperature and room temperature need to be monitored carefully and alteration in room temperature made to compensate for changes in core body temperature. Fluid loss during such illness can be considerable and needs to be replaced either orally or parenterally. The illness is usually short, but in cases where recovery is slow, nutritional support may be necessary. The eroded skin is at risk of becoming secondarily infected; careful, considerate nursing can reduce sources of infection.

Corticosteroids are contraindicated in the management of SSSS as they are associated with a worsening of the disease.[10,37]

Screening should be considered if a number of cases have arisen simultaneously. Swabs from the anterior nares and any eroded skin should be taken from suspected asymptomatic carriers. If positive, the individual should be removed from looking after children less than 2 years of age and treated with an oral β-lactamase–resistant semisynthetic penicillin, such as flucloxacillin.[105]

9. Prognosis

Mortality in childhood SSSS is approximately 4% and is associated with extensive skin involvement, overwhelming sepsis and the resultant electrolyte imbalance.[16] However, the mortality rate in adults is reported to be greater than 60%,[37] much of which may be attributed to the underlying irreversible factors that predispose to the illness.

10. Conclusions

Our understanding of SSSS has greatly improved since Baron Ritter von Ritershain first described the disorder. Social improvements and hygiene have led to a dramatic fall in the number of cases. Better understanding of the toxins responsible has significantly furthered our knowledge of the disorder. SSSS has a characteristic clinical presentation in children allowing for early recognition. However, there is a spectrum of disease and there are likely to be a number of milder cases of adult SSSS that remain undiagnosed. Treatment is usually straightforward, when there is no coexistent morbidity and the presentation is mild, but can be demanding if the patient is particularly ill. SSSS is still associated with mortality, particularly when it occurs in adults.

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References

1. Ritter von Rittershain G. Die exfoliativa dermatitis jüngerer Säulinge. Centralz Kinderheilk 1878; 2: 3-23
2. Lyell A. Toxic epidermal necrolysis: an eruption resembling scalding of the skin. Br J Dermatol 1956; 68: 355-61
3. Lyell A, Dick HM, Alexander JO. Outbreak of toxic epidermal necrolysis associated with staphylococci. Lancet 1969; I: 787-9
4. Lyell A. A review of toxic epidermal necrolysis in Britain. Br J Dermatol 1967; 79: 662-71
5. Jefferson J. Lyell's toxic epidermal necrolysis: a staphylococcal aetiology? BMJ 1967; 555: 802-4
6. Tyson RG, Ushinski SC, Kisilevsky R. Toxic epidermal necrolysis (the scalded skin syndrome): its association in two cases with pathogenic staphylococci and its similarity in infancy to Ritter's disease. Am J Dis Child 1966; 111: 386-92

7. Messaritakis J. Toxic epidermal necrolysis in children: description of 4 cases. Ann Paediatr 1966; 207 (4): 236-46
8. Melish ME, Glasgow LA. The staphylococcal scalded-skin syndrome. N Engl J Med 1970; 282: 1114-9
9. Kapral FA, Miller MM. Product of Staphylococcus aureus responsible for the scalded skin syndrome. Infect Immun 1971; 4: 541-5
10. Melish ME, Glasgow LA, Turner MD. Staphylococcal scalded skin syndrome: isolation and partial characterisation of the exfoliative toxin. J Infect Dis 1972; 125: 129-40
11. Elias PM, Fritsch P, Mittermayer H, et al. Experimental staphylococcal toxic epidermal necrolysis (TEN) in adult humans and mice. J Lab Clin Med 1974; 84: 414-24
12. Lyell A. The staphylococcal scalded skin syndrome a historical perspective: emergence of dermopathic strains of Staphylococcal aureus and the discovery of the epidermolytic toxin. J Am Acad Dermatol 1983; 9: 285-94
13. Levine G, Norden CW. Staphylococcal scalded skin syndrome in an adult. N Engl J Med 1972; 287: 1339-40
14. Patel GK, Varma S, Finlay AY. Staphylococcal scalded skin syndrome in healthy adults. Br J Dermatol 2000; 142 (6): 1253-5
15. Amagai M, Matsuyoshi N, Wang ZH, et al. Toxin in bullous impetigo and staphylococcal scalded skin syndrome targets desmoglein 1. Nature Med 2000; 6: 1275-7
16. Elias PM, Fritsch P, Epstein EV. Staphylococcal scalded skin syndrome: clinical features, pathogenesis, and recent microbiological and biochemical developments. Arch Dermatol 1977; 113: 207-19
17. Elias PM, Levy SW. Bullous impetigo: occurrence of scalded skin syndrome in an adult. Arch Dermatol 1976; 112: 856-8
18. Falk DK, King LE. Criteria for the diagnosis of Staphylococcal scalded skin syndrome in adults. Cutis 1983; 31: 431-4
19. Lowney ED, Baublis JV, Kreye GM, et al. The scalded skin syndrome in small children. Arch Dermatol 1967; 95: 359-69
20. Moss C, Gupta E. The Nikolsky sign in staphylococcal scalded skin syndrome [letter]. Arch Dis Child 1998; 79: 290
21. Shelley ED, Shelley WB, Talanin NY. Chronic staphylococcal scalded skin syndrome. Br J Dermatol 1998; 139: 319-24
22. Reid LH, Weston WL, Humbert JR. Staphylococcal scalded skin syndrome: adult patient with deficient cell mediated immunity. Arch Dermatol 1976; 112: 1275-9
23. Fine JD, Harrist TJ, Radford MJ. Adult scalded skin syndrome fatally complicated by mixed gram-negative sepsis and cellulitis. Cutis 1981; 27: 162-7
24. Norden CW, Mendelow H. Staphylococcal scalded skin syndrome in adults [letter]. N Engl J Med 1974; 290: 577
25. Todd JK. Staphylococcal toxin syndromes. Annu Rev Med 1985; 36: 337-47
26. Amon RB, Dimond RL. Toxic epidermal necrolysis: rapid differentiation between staphylococcal- and drug-induced disease. Arch Dermatol 1975; 111: 1433-7
27. Dimond RL, Wolff HH, Braun-Falco O. The staphylococcal scalded skin syndrome: an experimental histochemical and electron microscopy study. Br J Dermatol 1977; 96: 483-92
28. Robinson ND, Hashimoto T, Amagai M, et al. The new pemphigus variants. J Am Acad Dermatol 1999; 40: 649-71
29. Breathnach SM, McGibbon DH, Ives FE, et al. Carbamazepine (Tegretol) and toxic epidermal necrolysis: report of three cases with histopathological observations. Clin Exp Dermatol 1982; 7: 585-91
30. Gillespie WA, Pope RC, Simpson K. Pemphigus neonatorum caused by Staphylococcal aureus type 71. BMJ 1957; 1: 1044-6
31. Willard D, Montell H, Piermont Y, et al. Exfoliatine dans les staphylococcies neonatales. Nouv Presse Med 1982; 11: 3769-71
32. Parker MT. Some cultural characteristics of Staphylococcus aureus strains from superficial skin infections. J Hyg (Lond) 1958; 56: 238-53
33. Arbuthnott JP, Kent K, Lyell A, et al. Toxic epidermal necrolysis produced by an extracellular product of Staphylococcus aureus. Br J Dermatol 1971; 85: 145-9
34. Lina G, Gillet Y, Vadenesch F, et al. Toxin involvement in Staphylococcal scalded skin syndrome. Clin Infect Dis 1997; 25: 1369-73
35. Arbuthnott JP, Gemmel CG, Kent J, et al. Haemolysin and enzyme patterns of coagulase-positive staphylococci isolated from toxic epidermal necrolysis, Ritter's disease and impetigo contagiosa. J Med Microbiol 1969; 2: 479-87
36. Dancer SJ, Garratt R, Saldanha J, et al. The epidermolytic toxins are serine proteinases. FEBS Lett 1990; 268: 129-32
37. Wiley BB, Allman S, Rogolsky M, et al. Staphylococcal scalded skin syndrome: potentiation by immunosuppression in mice; toxin-mediated exfoliation in a healthy adult. Infect Immun 1974; 9: 636-40
38. Rogolosky M, Wiley BB, Glasgow LA. Phage group II Staphylococcal strains with chromosomal and extra-chromosomal genes for exfoliative toxin production. Infect Immun 1976; 13: 44-52
39. Oono T, Kanzaki H, Yoshioka T, et al. Staphylococcal scalded skin syndrome in an adult: identification of exfoliative toxin A and B genes by polymerase chain reaction. Dermatology 1997; 195: 268-70
40. Criber B, Piemont Y, Grosshans E. Staphylococcal scalded skin syndrome in adults. J Am Acad Dermatol 1994; 30: 319-24
41. Kawabata A, Ichiyama S, Iinuma Y, et al. Exfoliative toxin detection using reverse passive latex agglutination: clinical and epidemiologic application. J Clin Microbiol 1997; 35: 1984-7
42. Sarai Y, Nikahara H, Ishikawa T, et al. A bacteriological study on children with staphylococcal toxic epidermal necrolysis in Japan. Dermatologica 1977; 154: 161-7
43. Murono K, Fujita K, Yoshika H. Microbiological characteristics of exfoliative toxin-producing Staphylococcus aureus. Paediatr Infect Dis J 1988; 7: 313-5
44. De Azevedo JCS, Arbuthnott JP. Assays for epidermolytic toxin of Staphylococcus aureus. Methods Enzymol 1988; 165: 333-8
45. Rifai S, Barbancon V, Prevost G, et al. Synthetic exfoliative toxin A and B DNA probes for detection of toxigenic Staphylococcus aureus strains. J Clin Microbiol 1989; 27: 504-6
46. Murono K, Fujita K, Yoskioka H. Detection of staphylococcal exfoliative toxin by slide latex agglutination. J Clin Microbiol 1988; 26: 271-4
47. Hoeger PH, Elsner P. Staphylococcal scalded skin syndrome: transmission of the exfoliatin-producing Staphylococcus aureus by asymptomatic carriers. Pediatr Infect Dis 1988; 7: 340-2
48. Dave J, Reith S, Nash JQ, et al. A double outbreak of exfoliative toxin-producing strains of Staphylococcus aureus in a maternity unit. Epidemiol Infect 1994; 112: 103-14
49. Curran JP, Al-Sahili FL. Neonatal staphylococcal scalded skin syndrome: massive outbreak due to an unusual phage type. Paediatrics 1980; 66: 285-90
50. Opal SM, Johnson-Winegar AD, Cross AS. Staphylococcal scalded skin syndrome in two immunocompetent adults caused by exfoliating B-producing Staphylococcus aureus. J Clin Microbiol 1988; 26: 1283-6
51. Diem E, Konrad K, Graninger W. Staphylococcal scalded skin syndrome in an adult with fatal disseminated sepsis. Acta Derm Venereol (Stockh) 1982; 62: 295-9
52. Petzelbauer P, Konrad K, Wolff K. Staphylococcal scalded skin syndrome in 2 adults with acute kidney failure. Hautarzt 1989; 40: 90-3
53. Rothenberg R, Renna F, Drew T. Staphylococcal scalded skin syndrome in an adult. Arch Dermatol 1973; 108: 408-10
54. Neefe LI, Tuazon CV, Cardella TA, et al. Staphylococcal scalded skin syndrome in adults: case report and review of the literature. Am J Med Sci 1979; 277: 99-110

55. Borchers SL, Gomez EC, Isseroff RR. Generalized staphylococcal scalded skin syndrome in an anephric boy undergoing hemodialysis. Arch Dermatol 1984; 120: 912-8
56. Donohue D, Robinson B, Goldberg NS. Staphylococcal scalded skin syndrome in a woman with chronic renal failure exposed to human immunodeficiency virus. Cutis 1991; 47: 317-8
57. Elsner P, Hartmann AA. Epidemiology of ETA- and ETB- producing staphylococci in dermatological patients [abstract]. Zentralbl Bakteriol Mikrobiol Hyg [A] 1988; 268: 534
58. Arbuthnott JP. Characterisation of the epidermolytic toxins of Staphylococcus aureus. In: Macdonald A, Smith G, editors. The Staphylococci: proceedings of the Alexander Ogston Centennial Conference. Aberdeen: Aberdeen University Press, 1981: 109-18
59. Acland KM, Darvay A, Griffin C, et al. Staphylococcal scalded skin syndrome in an adult associated with methicillin-resistant Staphylococcus aureus. Br J Dermatol 1999; 140: 518-20
60. McLay ALC, Arbuthnott JP, Lyell A. Action of Staphylococcal epidermolytic toxin on mouse skin: an electron microscopy study. J Invest Dermatol 1975; 65: 423-8
61. Sato H, Matsumori Y, Tanabe T, et al. A new type of staphylococcal exfoliative toxin from a Staphylococcus aureus strain isolated from a horse with phlegmon. Infect Immun 1994; 62: 3780-5
62. Lillibridge CB, Melish ME, Glasgow LA. Site of action of exfoliative toxin in the staphylococcal scalded skin syndrome. Pediatrics 1972; 50: 728-38
63. Kapral FA, Miller NM. Product of Staphylococcal aureus responsible for the staphylococcal scalded skin syndrome. Infect Immun 1971; 4: 541-5
64. Arbuthnott JP, Kent J, Lyell A, et al. Studies of staphylococcal toxins in relation to toxic epidermal necrolysis: the scalded skin syndrome [supplement]. Br J Dermatol 1972; 86: s35-9
65. Wuepper KD, Dimond RL, Knutson DD. Studies of the mechanism of epidermal injury by Staphylococcal epidermolytic toxin. J Invest Dermatol 1975; 65: 191-200
66. Melish ME, Chen FS, Sprouse S, et al. Epidermolytic toxin in staphylococcal infection: toxin levels and host response. Zentralbl Bakteriol Mikrobiol Hyg Suppl 1981; 10: 287-98
67. Bailey CJ, de Azavedo J, Arbuthnott JP. A comparative study of two serotypes of epidermolytic toxin from Staphylococcus aureus. Biochim Biophys Acta 1980; 624: 111-20
68. Kondo I, Sakurai S, Sarai Y. New type of exfoliatin obtained from staphylococcal strains, belonging to phage groups other than group II, isolated from patients with impetigo and Ritter's disease. Infect Immun 1974; 10: 851-61
69. Sakurai S, Suzuki H, Kondo I. DNA sequencing of the eta gene coding for Staphylococcal exfoliative toxin serotype A. J Gen Microbiol 1988; 134: 711-7
70. Lee CY, Schmidt JJ, Johnson-Winegar AD, et al. Sequence determination and comparison of exfoliative toxin A and B genes from Staphylococcal aureus. J Bacteriol 1987; 169: 3904-9
71. O'Toole PW, Foster TJ. Nucleotide sequence of the epidermolytic toxin A gene of Staphylococcus aureus. J Bacteriol 1987; 169: 3910-5
72. Sakuria S, Suzuki H, Kondo I. Cloning of the gene coding for Staphylococcal exfoliative toxin A and its expression in Escherichia coli. FEMS Microbiol Lett 1987; 42: 63-7
73. Smith TP, John DA, Bailey CJ. The binding of epidermolytic toxin from staphylococcus aureus to mouse epidermal tissue. Histochem J 1987; 19: 135-49
74. Gentihomme E, Faure M, Piemont Y, et al. Action of staphylococcal exfoliative toxins on epidermal cell cultures and organotypic skin. J Dermatol 1990; 17: 526-32
75. Vath GM, Earhart CA, Rago JV, et al. The structure of the superantigen exfoliative toxin A suggests a novel regulation as a serine protease. Biochemistry 1997; 36: 1559-66
76. Prevost G, Rifai S, Chaix ML, et al. Functional evidence that Ser-195 residue of Staphylococcal exfoliative toxin A is essential for biological activity. Infect Immun 1991; 59: 3337-9
77. Redpath MB, Foster TJ, Bailey CJ. The role of serine protease active site in the mode of action of epidermolytic toxin of S. aureus. FEMS Microbiol Lett 1991; 81: 151-6
78. Jaulhac B, Piemont Y, Prevost G. Staphylococcal exfoliative toxins induce proteolytic activity when combined with epidermis. In: Mollby R, Flock JI, Nord CE, et al., editors. Staphylococci and staphylococcal infections. New York: Gustav Fischer Verlag, 1994: 280-2
79. Barbosa JARG, Saldanaha JW, Garratt RC. Novel features of serine protease active sites and specificity pockets: sequence analysis and modelling studies of glutamate-specific endopeptidases and epidermolytic toxins. Protein Eng 1996; 9: 591-601
80. Rago JV, Vath GM, Tripp TJ, et al. Staphylococcal exfoliative toxins cleave alpha- and beta-melanocyte-stimulating hormones. Infect Immun 2000; 68: 2366-8
81. Mahoney MG, Wang Z, Rothenberger K, et al. Explanation for the clinical and microscopic localization of lesions in pemphigus foliaceous and vulgaris. J Clin Invest 1999; 103: 461-8
82. Marrack P, Kappler J. The staphylococcal enterotoxins and their relatives. Science 1990; 346: 471-3
83. Khuong MA, Chosidow O, Solh NE, et al. Staphylococcal scalded skin syndrome in an adult: possible influence of non-steroidal anti-inflammatory drugs. Dermatology 1993; 186: 153-4
84. Haas Baker D, Wuepper KD, Rasmussen JE. Staphylococcal scalded skin syndrome: detection of antibody to epidermolytic toxin by a primary binding assay. Clin Exp Dermatol 1978; 3: 17-24
85. Wiley B, Glasgow L, Rogolsky M. Studies on staphylococcal scalded skin syndrome (SSSS): isolation and purification of toxin and development of a radioimmunobinding assay for antibodies to exfoliative toxin (ET). In: Jeljaszewicz J, editor. Staphylococci and staphylococcal diseases. Stuttgart: Gustav Fischer Verlag, 1976: 499-516
86. Beer B, Wilson B. Adult staphylococcal scalded skin syndrome. Int J Dermatol 1990; 29: 428-9
87. Herzog JL, Sexton M. Desquamative rash in an immunocompromised adult. Arch Dermatol 1990; 26: 815-9
88. Trentham DE, Silvermann HA, Townes AS. Cause of adult toxic epidermal necrolysis [letter]. N Engl J Med 1975; 292: 870
89. Saiag P, Caumes E, Roujeau JC, et al. Epidermolyse staphylococcique (syndrome de Lyell staphylococcique) de l'adult: 2 cas. Ann Dermatol Venereol 1988; 115: 1164-6
90. Fritsch P, Elias P, Varga J. The fate of Staphylococcal exfoliatin in newborn and adult mice. Br J Dermatol 1976; 95: 275-84
91. Kirmani N, Tauzon CU, Murray HW, et al. Staphylococcus aureus carriage rate of patients receiving long term haemodialysis. Arch Intern Med 1978; 138: 467-75
92. Rothenburg R, Renna FS, Drew TM, et al. Staphylococcal scalded skin syndrome in an adult. Arch Dermatol 1973; 108: 408-10
93. Epstein Jr EH, Flynn P, Davis RS. Adult toxic epidermal necrolysis and fatal staphylococcal septicaemia. JAMA 1974; 229: 425-7
94. O'Keefe R, Dagg JH, Mackie RM. The staphylococcal scalded skin syndrome in two elderly immunocompromised patients. BMJ 1987; 295: 179-80

95. Roeb E, Schonfelder T, Matern S, et al. Staphylococcal scalded skin syndrome in an immunocompromised adult. Eur J Clin Microbiol Infect Dis 1996; 15: 499-503
96. Strumia R, Bedetti A, Cavazzini L. Staphylococcal scalded skin syndrome in corso di AIDS. G Ital Dermatol Venereol 1990; 125: 461-4
97. Farrell AM, Ross JS, Umasankar S, et al. Staphylococcal scalded skin syndrome in an HIV-1 seropositive man. Br J Dermatol 1996; 134: 962-5
98. Hawley HB, Aronson MD. Scalded skin syndromes in adults. N Engl J Med 1972; 288: 130
99. Melish ME, Chen FS, Sprouse S, et al. Epidermolytic toxin in staphylococcal infection: toxin levels and host response. Zentralbl Bakteriol Mikrobiol Hyg Suppl 1981; 10: 287-98
100. Ridgway HB, Lowe NJ. Staphylococcal scalded skin syndrome in an adult with Hodgkin's disease. Arch Dermatol 1979; 115: 589-90
101. Melish ME, Glasgow LA. The staphylococcal scalded skin syndrome: the expanded clinical syndrome. J Paediatr 1971; 78: 958-67
102. Rassmussen JE. Toxic epidermal necrolysis: a review of 75 cases in children. Arch Dermatol 1975; 111: 1135-9
103. Rudolph RI, Shwartz W, Leyden JJ. Treatment of staphylococcal toxic epidermal necrolysis. Arch Dermatol 1974; 110: 559-62
104. Yokota S, Imagawa T, Katakura S, et al. Staphylococcal scalded skin syndrome caused by exfoliative toxin B-producing methicillin-resistant Staphylococcus aureus [letter]. Eur J Paediatr 1996; 155: 722
105. Mackenzie A, Johnson W, Heyes B, et al. A prolonged outbreak of exfoliative toxin A-producing Staphylococcus aureus in a newborn nursery. Diagn Microbiol Infect Dis 1995; 21: 69-75

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