

CURRENT TOPIC

Staphylococcal scalded skin syndrome

Shamez Ladhani, Robert W Evans

The disease

Staphylococcal scalded skin syndrome (SSSS) is the clinical term used for a spectrum of blistering skin diseases induced by the exfoliative (epidermolytic) toxins (ET) of *Staphylococcus aureus*.¹ Current synonyms include Ritter's disease, bullous impetigo, pemphigus neonatorum, and staphylococcal scarlatiniform rash. It is a disease primarily affecting infants and young children,² but cases have been reported in adults.³ It seems that the location of lesions depends on age. In neonates, the lesions are mostly found on the perineum or periumbilically, or both, while the extremities are more commonly affected in older children.² The disease begins with erythema and fever, followed by formation of large fluid filled bullae which quickly rupture on slightest pressure (Nikolsky sign) to leave extensive areas of denuded skin.

The form and severity of SSSS will vary with the route of delivery of the toxin to the skin, ranging from the localised bullous impetigo to generalised SSSS involving the entire skin surface.^{2–4} In the latter, patients are susceptible to poor temperature control, extensive fluid losses, and secondary infections. They may also develop sepsis and present with hypotension, neutropenia, and respiratory distress.⁵ Antibiotic treatment with β -lactamase resistant semisynthetic penicillins such as flucloxacillin is usually effective.^{3–6} Outbreaks of SSSS involving a large number of babies in neonatal wards are not uncommon and may persist for a long time if carriers of toxin producing *S aureus* are not rapidly identified and treated.^{6–9}

Considering the severity of the disease and the amount of published work, it is surprising how little progress has been made in understanding the mode of action of the toxin and the epidemiology of the disease. Much work over the years on SSSS has been uneventful and repetitive—a large outbreak or a fatal outcome usually results in a surge of interest in the disease, which soon declines until the next event. There have been no major breakthroughs in management or prevention over the past 25 years. It is true that because of the ease of treatment of SSSS with effective antibiotics and the lack of long term sequelae such as scarring, there is very little pressure for research into the disease and the toxins that cause it. However, the mortality is still 3% in children,^{10–11} and over 50% in adults, reaching almost 100% in those with underlying disease (see below), despite antibiotic treatment.³

Potential problems with antibiotic resistance have also recently arisen with the isolation of a methicillin resistant toxin producing strain of *S aureus* in a case of SSSS in Japan.¹²

The toxins

The role of the exfoliative toxins in SSSS was demonstrated as far back as 1970,¹ but their mechanism of action remains elusive 25 years later, even though their physicochemical properties and, more recently, aspects of their mode of action have been extensively studied. The two known toxins (ETA and ETB) act specifically in the zona granulosa of the epidermis,¹³ and even intraperitoneal inoculation will result in exfoliation. Immunocytochemical studies have shown that the toxin binds to the filaggrin group of proteins in keratohyalin granules,¹⁴ and because filaggrins act as intracellular anchors of desmosomes, many investigators have speculated that epidermal splitting is a result of rupture of these desmosomes, probably from proteolytic activity of the toxins.^{15–17} The toxins in their native form, however, do not have any significant proteolytic activity,^{18–19} and the hypothesis that they may be serine proteases comes from indirect evidence: (1) both toxins show significant sequence homology with the staphylococcal V8 protease, particularly in the region of the serine–aspartic acid–histidine catalytic triad that forms the active site of trypsin-like serine proteases¹⁵; (2) replacing any of the three amino acids that form the catalytic triad of the toxins results in complete loss of biological activity when injected into newborn mice^{16–19}; (3) incubation of ETA with neonatal mouse epidermis¹⁸ or neonatal mouse epidermal extract¹⁹ results in the induction of caseinolytic activity in the supernatant; and (4) recent computer modelling²⁰ and crystallographic studies^{21–22} on the three dimensional structure of the toxins have revealed a high degree of structural similarity with known glutamate specific trypsin-like serine proteases. Deletion studies have shown that the highly charged amino terminal of the exfoliative toxins is essential for their activity,²² and recent structural studies have led to speculation that this region may be responsible for binding an epidermal receptor, which in turn may result in a conformational change that exposes the toxin's active catalytic site.²¹

Division of
Biochemistry and
Molecular Biology,
UMDS, Guy's
Campus, London
Bridge, London
S Ladhani
R W Evans

Correspondence to:
Dr Shamez Ladhani, 65
Littlemeade, Cold Harbour
Estate, Mottingham, London
SE9 3ED, UK

Epidemiology

Staphylococcus aureus is a Gram positive coccus which colonises the nose, perineum, axillae, eyes, wound sites, and toe webs.²³ Two toxin serotypes are known—ETA and ETB—but others may exist.²⁴ In the West, 80–85% of toxin producing *S aureus* belong to phage group II,³ and around 90% of toxin producing strains produce ETA.²⁵ In contrast, in Japan there is a predominance of ETB producing strains, which are less likely to be of phage group II.^{26,27} A recent Nigerian study showed that healthy animals can carry exfoliatin producing *S aureus*,²⁸ and a previous study identified toxin producing strains in inanimate objects such as ventilation shafts in a hospital.²⁹ Both may act as reservoirs of infection, but their impact on human SSSS has not been determined.

Large epidemiological studies have found toxin producing strains of *S aureus* in 5.1% of 944 isolates from 577 dermatological patients screened,¹⁰ 6.2% of 2362 isolates from hospital inpatients,³⁰ 3% of isolates from 500 antenatal women,³¹ and 4.0% of isolates from various clinical sources in Nigeria.²⁸ Hargiss and Larson found that up to 60% of newborn babies discharged from the hospitals may be nasal carriers of *S aureus*.³² If approximately 5% of the strains produce the exfoliative toxins, then as many as 3% of all neonates may carry toxin producing strains of *S aureus*.

However, the incidence of SSSS does not seem to be as common as might be expected. This might be the result of any combination of poor data collection and reporting of the disease, a lower than reported prevalence of toxin producing *S aureus* carriage, or a low incidence of disease in carriers, possibly because of high levels of protective antitoxin antibodies in the population. Studies in 1981 showed ETA antibody in 88% of cord blood samples, reflecting maternal antibody status.¹¹ This level dropped to 30% at 3 months to 2 years, then rose steadily to 91% at 40 years. In cases of generalised SSSS, ETA antibody was absent in acute sera (five days) and present in convalescent sera (14 days). This contrasts with localised infection, when antibody was present in over 60% of acute samples (four to 10 days) but was no predictor of spread of disease. Perhaps maternal antibodies play an important role in preventing SSSS, as has been shown in mice,³³ and if so breast feeding may be protective.

Factors other than antibodies may also govern the development and severity of SSSS. Organism factors may include subtle differences in *S aureus* strains or the toxins themselves, requirement of a triggering factor for toxin production, requirement of a cofactor for the toxins, or the quantity of toxin in the blood. Host factors may include an inappropriate immune response to bacteria or their toxins, the presence of concurrent infections which would lower the host immune response, or a genetically variable site of action of the exfoliative toxins, which would make some individuals more susceptible than others.

Healthy adults rarely develop SSSS, and the only two reported cases have been due to ETB,³ although it is not known whether this is a coincidence or whether ETB is more commonly able to affect healthy adults. Reported risk factors for adult SSSS include immunosuppression (including immunosuppressive drugs and AIDS), renal failure, malignant disease, chronic alcohol abuse, and intravenous drug addiction.³ However, it is still not clear whether the disease is the result of a higher carriage rate of toxin producing *S aureus*, increased susceptibility to the toxins, lack of protective antitoxin antibodies, or just a manifestation of a generalised increase in the risk of infections.

Diagnosis

In the United Kingdom, SSSS diagnosis is currently based mainly on clinical grounds, supported by the presence of *S aureus* in nasal, conjunctival, pharyngeal, umbilical, or other swabs, although these criteria are not always reliable.³⁴ If confirmation of the diagnosis is required, or when outbreaks occur, isolates can be sent to the Public Health Laboratory (PHL), London, where the *S aureus* will be phage typed (this service is not routinely available in hospital laboratories). The presence of isolates in phage group II will strongly support the diagnosis of SSSS, even though other phage types have been shown to produce an identical clinical picture.³⁵ If further confirmation of the diagnosis is required, the PHL may test for toxins using the immunological Ouchterlony method, which lacks sensitivity and specificity.

Other detection systems have been developed for the exfoliative toxins, including serological methods of gel immunoprecipitation, radioimmunological assays, enzyme linked immunosorbent assays, and detection of gene sequences by DNA hybridisation and polymerase chain reaction.³⁶ False positive results may occur in serological studies due to protein A, a 42 kDa protein produced by over 90% of *S aureus*, which binds non-specifically to the constant (Fc) domain of immunoglobulins.³⁷ These detection systems were developed for use in research laboratories rather than clinical settings and tend to be either very expensive or too time consuming for routine use.

Research

While a great deal of information is still lacking, two particular areas of research merit more attention: the development of a standard assay for the exfoliative toxins, and elucidation of their mechanism of action.

DEVELOPING A STANDARDISED ASSAY

The availability of a sensitive, specific, reliable clinical diagnostic kit which is simple to use would considerably alter the management of SSSS. Such a kit would allow a confirmed diagnosis of SSSS, with simple tests to detect toxin levels in the blood or bullae, to be available within a few hours. Differential diagnosis of generalised exfoliation includes drug induced and virus mediated toxic epidermal

necrosis, burns, epidermolysis bullosa, bullous erythema multiforme, listeria and syphilis infections, diffuse cutaneous mastocytosis, and graft versus host rejection.³⁸ Rapid diagnosis of individual cases, particularly in adults where mortality rates are high, is important for initiating appropriate treatment and reducing mortality. Similarly, the rapid identification and treatment of asymptomatic carriers—who may be numerous—should reduce the risk of large outbreaks of infection.

The diagnostic kit would improve our understanding of the organism responsible, its toxins, and the diseases they cause. For example, simple epidemiological data on SSSS, such as age distribution, sex ratio, ethnic susceptibilities, and community as well as nursery attendant carrier rates, are still lacking. The kit would also speed up research into the possible role of staphylococcal toxins in other conditions such as eczema³⁹ and sudden infant death syndrome.⁴⁰

ELUCIDATING THE MECHANISM OF ACTION

All the evidence for the exfoliative toxins being glutamate specific trypsin-like serine proteases is indirect and speculative and needs to be substantiated with more research. The problem lies in the lack of a suitable model to study the mechanism of action of the toxins. The gold standard model still remains newborn¹ or hairless⁴¹ mice, developed over two decades ago. Since then, various attempts have been made to develop a simpler and more humane model to work on; human epidermis from surgery, keratinocyte cultures, and mouse epidermis have been used to demonstrate epidermal splitting at the zona granulosa.^{13 14 42 43} All these assays are difficult to perform and replicate, thus hampering research.

However, research using the neonatal mouse epidermis assay^{18 19} could be extended to investigate whether the exfoliative toxins are indeed serine proteases and whether they bind to any receptors,⁴⁴ and to elucidate events following binding. The model could also be used to determine any changes occurring in ETA, including a conformational change after receptor binding to expose the active catalytic site, as has recently been speculated from structural models.^{21 22} The main difficulty is the use of mouse epidermis, but keratinocytes cell cultures, for example, may provide an alternative substitute.

Understanding the mechanism of action of the toxins has several important implications. For example, their ability to target a specific layer within the epidermis could be used to investigate the normal physiology of the skin by identifying, marking, and isolating specific groups of cells and cell structures. Similarly, if the toxins' targeting domain can be identified, it may be possible to attach and deliver potent drugs, such as chemotherapeutic agents, to specific sites within the skin, thereby reducing the dose required and systemic side effects. Other toxins, such as diphtheria and pseudomonas exotoxin A,⁴⁵ have already served a similar purpose and provided novel treatments for various carcinogenic, immunological, and

haematological disorders. Furthermore, if antitoxin antibodies are shown to protect against SSSS, then inactive toxoids may be developed to provide active immunisation in susceptible populations.

The localised blistering seen in most healthy individuals with SSSS could be exploited to produce a localised and controlled exfoliation—for example, to remove a superficial offending skin lesion.

Finally, discovering the mechanism of action of these toxins may lead to the development of effective antitoxins. Given concurrently with antibiotics, antitoxins may abort exfoliation if SSSS is diagnosed early, or may decrease the extent of exfoliation in severe cases, as may occur in late presentation or delayed diagnosis of the disease, in antibiotic resistant *S aureus* strains that do not respond to conventional antibiotics and in patients with underlying disease, where mortality rates are high.

Conclusions

Although SSSS is relatively uncommon, usually easily diagnosed on clinical grounds, and readily treated with conventional antibiotics, it is important to emphasise that at present mortality rates are still unacceptably high, outbreaks are difficult to control, and the secondary complications, which are particularly common in neonates, can often be lethal. Furthermore, clinicians should be aware of three recently emerging trends. Firstly, although phage group II staphylococci only rarely develop antibiotic resistance,³ one such case has already been described recently,¹² and it is well known that hospital outbreaks of multiresistant organisms are difficult and expensive to control and carry a high mortality rate.

Secondly, in the 1980s several studies showed that the use of antiseptic neonatal umbilical cord care delayed the time of cord separation,⁴⁶⁻⁴⁸ and this may produce parental concern and increase midwives' workload. Since then, there has been a gradual decline in the use of antiseptic umbilical cord care in the United Kingdom. However, several studies have shown that this practice has led to a significant increase in staphylococcal umbilical colonisation, which in turn may lead to an increase in neonatal infections, including SSSS and methicillin resistant *S aureus* outbreaks.⁴⁹⁻⁵¹

Finally, the recent pressure to discharge patients early from hospitals, particularly mothers and their newborn babies, may serve to dissipate outbreaks (including SSSS)—caused by hospital staff in close contact with neonates—into the community.⁶ While individual cases can easily be treated by the primary health care team, delays in recognising an outbreak mean that carriers still working in the hospital will continue to infect more patients until identified, isolated, and treated. Staff should therefore ensure rigorous aseptic technique with hospital patients, particularly with neonates, and clinicians should beware of a possible outbreak, even if patients present with infection after hospital discharge.

In conclusion, the chapter on SSSS is by no means closed. Much work has to be done by both researchers and clinicians, and there is now added pressure to do so more quickly. SSSS researchers should be encouraged to publish more of their work, including negative findings, while clinicians should be collecting and combining more data and performing simple epidemiological studies on the disease and the organism responsible. It is only through such collaborative work that wasteful repetitive research will be reduced and a more integrated approach taken to tackle the disease once and for all.

This work is the result of ideas and suggestions derived from group discussions and debates held within the Division of Biochemistry and Molecular Biology and the Division of Microbiology at UMDS, London. We would specifically like to thank Dr S Poston, Dr C L Joannou, and Miss J Cameron. The work on SSSS has been supported by the Trustees of Guy's Hospital, The Clothworkers' Foundation, and The Agakhan Foundation.

- 1 Melish ME, Glasgow LA. The staphylococcal scalded skin syndrome: development of an experimental model. *N Engl J Med* 1970;282:1114-9.
- 2 Melish ME. Staphylococci, streptococci and the skin: review of impetigo and staphylococcal scalded skin syndrome. *Semin Dermatol* 1982;1:101-9.
- 3 Cribrier B, Piemont Y, Grosshans E. Staphylococcal scalded skin syndrome in adults: a clinical review illustrated with a new case. *J Am Acad Dermatol* 1984;30:319-24.
- 4 Itani O, Crump R, Mimouni F, et al. Picture of the month: SSSS. *Am J Dis Child* 1992;146:425-6.
- 5 Loughead JL. Congenital staphylococcal scalded skin syndrome: report of a case. *Pediatr Infect Dis J* 1992;11:413-4.
- 6 Bell FG, Fenton PA. Early hospital discharge and cross-infection. *Lancet* 1993;342:120.
- 7 Dancer SJ, Simmons NA, Poston SM, et al. Outbreak of staphylococcal scalded skin syndrome among neonates. *J Infect* 1988;16:87-103.
- 8 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.
- 9 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.
- 10 Gemell CG. Staphylococcal scalded skin syndrome. *J Med Microbiol* 1995;43:318-27.
- 11 Melish ME, Chen FS, Sprouse S, et al. Epidermolytic toxin in staphylococcal infection: toxin levels and host response. In: Jelijaszewicz J, ed. *Staphylococci and staphylococcal infection (Zbl Bakt Suppl 10)*. Stuttgart: Gustav Fischer, 1981:287-98.
- 12 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 Pediatr* 1996;155:722.
- 13 Dimond RL, Wolff HH, Braun-Fulco O. The staphylococcal scalded skin syndrome. An experimental histochemical and electron microscopic study. *Br J Dermatol* 1977;96:483-92.
- 14 Gentilhomme 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.
- 15 Dancer SJ, Garratt R, Saldanha J, et al. The epidermolytic toxins are serine proteases. *FEBS Lett* 1990;268:129-32.
- 16 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.
- 17 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.
- 18 Takiuchi I. Staphylococcal exfoliative toxin induces caseinolytic activity. *J Infect Dis* 1987;156:508-10.
- 19 Jaulhac B, Piemont Y, Prevost G. Staphylococcal exfoliative toxins induce proteolytic activity when combined with epidermis. In: Mollby, Flock, Nord, Christensson, eds. *Staphylococci and staphylococcal infections. Proceedings of the 7th International Symposium, Stockholm, June 29-July 3, 1992 (Zbl Bakt Suppl 26)*. Stuttgart: Gustav Fischer, 1994: 280-2.
- 20 Barbosa JARG, Saldanha 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 Engineering* 1996;9:591-601.
- 21 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.
- 22 Cavarelli J, Prevost G, Bourguet W, et al. The structure of *Staphylococcus aureus* epidermolytic toxin A, an atypical serine protease, at 1.7A resolution. *Structure* 1997;5:813-24.
- 23 Noble WC. Microbiology of human skin. *The micrococcae*. London: Lloyd-Luke, 1981:152-81.
- 24 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.
- 25 Willard D, Monteil H, Piemont Y, et al. L'exfoliatine dans les staphylococcies néonatales. *Nouv Presse Med* 1982;11:3769-71.
- 26 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.
- 27 Muroto K, Fujita K, Yoshioka H. Microbiological characteristics of exfoliative toxin-producing *Staphylococcus aureus*. *Pediatr Infect Dis J* 1988;7:313-5.
- 28 Adesiyun AA, Lenz W, Schaal KP. Exfoliative toxin production by *Staphylococcus aureus* strains isolated from animals and human beings in Nigeria. *Microbiologica* 1991;14:357-62.
- 29 Kaplan MH, Chmel H, Hsieh H, et al. Importance of exfoliative toxin A production by *Staphylococcus aureus* strains isolated from clustered epidemics of neonatal pustulosis. *J Clin Microbiol* 1986;23:83-91.
- 30 Piemont Y, Rasoamananjara D, Fouace JM, et al. Epidemiological investigation of exfoliative toxin-producing *Staphylococcus aureus* strains in hospitalized patients. *J Clin Microbiol* 1984;19:417-20.
- 31 Dancer SJ, Noble WC. Nasal, axillary, and perineal carriage of *Staphylococcus aureus* among women: identification of strains producing epidermolytic toxin. *J Clin Pathol* 1991;44:681-4.
- 32 Hargiss C, Larson E. The epidemiology of *Staphylococcus aureus* in a newborn nursery from 1970 through 1976. *Pediatrics* 1978;61:348-53.
- 33 Machida K. Immunological investigations on the pathogenesis of staphylococcal scalded skin syndrome. *Jpn J Clin Pathol* 1995;43:547-56.
- 34 Falk DK, King LE. Criteria for the diagnosis of staphylococcal scalded skin syndrome in adults. *Cutis* 1983;31:421-4.
- 35 Curran JP, Al-Salihi FL. Neonatal staphylococcal scalded skin syndrome: massive outbreak due to an unusual phage type. *Pediatrics* 1980;66:285-90.
- 36 De Azevedo JCS, Arbuthnott JP. Assays for epidermolytic toxin of *Staphylococcus aureus*. *Methods Enzymol* 1988;165:333-8.
- 37 Forsgren A. Significance of protein A production by staphylococci. *Infect Immun* 1970;2:672-3.
- 38 Easterley NB, Solomon LM. Neonatal dermatology II: blistering and scaling dermatoses. *J Pediatr* 1970;77:1075-88.
- 39 McFadden JP, Noble WC, Kemp RD. Superantigenic exotoxin-secreting potential of staphylococci isolated from atopic eczematous skin. *Br J Dermatol* 1993;128:631-2.
- 40 Malam JE, Carrick GF, Telford DR, et al. Staphylococcal toxins and sudden infant death syndrome. *J Clin Pathol* 1993;45:716-21.
- 41 Arbuthnott JP, Kent J, Noble WC. The response of hairless mice to staphylococcal epidermolytic toxin. *Br J Dermatol* 1973;88:481-5.
- 42 Lillibridge CB, Melish ME, Glasgow LA. Site of action of exfoliative toxin in the staphylococcal scalded skin syndrome. *Pediatrics* 1972;50:728-38.
- 43 Elias PM, Fritsch P, Dahl MV. Staphylococcal toxic epidermal necrolysis: pathogenesis and studies on the subcellular site of action of exfoliatin. *J Invest Dermatol* 1965;65:501-12.
- 44 Tanabe T, Sato H, Ueda K, et al. Possible receptor for exfoliative toxins produced by *Staphylococcus hyicus* and *Staphylococcus aureus*. *Infect Immun* 1995;63:1591-4.
- 45 Woodworth TG, Nichols JC. Recombinant fusion toxins—a new class of targeted biologic therapeutics. *Cancer Treat Res* 1995;68:145-60.
- 46 Lawrence CR. Effect of two different methods of umbilical cord care on its separation time. *Midwives Chron* 1982;95:204-5.
- 47 Mugford M, Somchiwong M, Waterhouse I. Treatment of umbilical cords: a randomized controlled trial to assess the effect of treatment methods on the work of midwives. *Midwifery* 1986;2:177-86.
- 48 Ronchea-Oms C, Hernandez C, Jimenez NV. Antiseptic cord care reduces bacterial colonisation but delays cord detachment. *Arch Dis Child* 1994;70:F70.
- 49 Watkinson M, Dyas A. *Staphylococcus aureus* still colonises the untreated neonatal umbilicus. *J Hosp Infect* 1992;21:131-6.
- 50 Allen KD, Ridgway EJ, Parsons LA. Hexachlorophane powder and neonatal staphylococcal infection. *J Hosp Infect* 1994;27:29-33.
- 51 Stark V, Harrison SP. *Staphylococcus aureus* colonization of the newborn in a Darlington hospital. *J Hosp Infect* 1992;21:205-11.