Recent developments in staphylococcal scalded skin syndrome

S. Ladhani

Department of Paediatrics, Guy's Hospital, London Bridge SE1 9RT, UK

Staphylococcal scalded skin syndrome describes a spectrum of superficial blistering skin disorders caused by the exfoliative toxins of *Staphylococcus aureus*. In its severe form, the exfoliation can spread to cover the entire body surface area. Two *S. aureus* exfoliative toxin serotypes affecting humans have been identified, but their purpose and mechanism of action have remained elusive. Based on their interaction with human and mouse epidermis, their three-dimensional structure and site-directed mutagenesis studies, it is speculated that they act as atypical serine proteases, and desmoglein-1 has now been identified as the specific epidermal substrate. Recent studies also suggest that the toxins may have a unique superantigenic activity. Clinically, new rapid diagnostic tests have been developed, including one that is able to detect the toxins directly from serum. With early diagnosis and appropriate management, mortality in children remains low and long-term complications are rare because the lesions are superficial and heal rapidly without scarring. In adults, however, the condition carries a mortality of almost 60% despite aggressive treatment, usually because of serious underlying illness. The recent developments in our understanding of the exfoliative toxins should lead to new and improved diagnostic and therapeutic strategies, including the use of specific antixoxins to prevent exfoliation.

Keywords Exfoliative toxins, ETA, ETB, desmoglein-1, diagnosis, treatment

Clin Microbiol Infect 2001; 7: 301–307

INTRODUCTION

Staphylococcal scalded skin syndrome (SSSS) describes a spectrum of superficial blistering skin disorders caused by the exfoliative toxins (also known as epidermolytic toxins, epidermolysins and exfoliatins) of *Staphylococcus aureus* [1,2]. Its severity varies from localized blisters to generalized exfoliation affecting the entire body surface [3]. While mortality is low with appropriate care in children, it can reach almost 60% in adults, who usually have an underlying illness [4]. The condition was first described by Baron von Rittershain, a German physician working in a Czechoslovakian foundling asylum in 1878 [5]. However, the toxins responsible were only identified in 1970 after Melish and Glasgow demonstrated that injecting newborn mice with *S. aureus* isolated from patients with SSSS resulted in mid-epidermal cleavage and exfoliation [6]. Since then, there have been several major breakthroughs in both our understanding of the exfoliative toxins responsible and the management of the condition [4]. The aim of this article is to review the clinical and microbiological aspects of SSSS, with particular emphasis on recent developments.

Corresponding author and reprint requests: S. Ladhani, Department of Paediatrics, Guy's Hospital, London SE1 9RT, UK.
Tel: +44 207 848 6482
Fax: +44 207 848 6485
E-mail: DrShamez@aol.com

PATHOGENESIS

Staphylococci and the exfoliative toxins

An association between generalized SSSS and *S. aureus* was proposed as far back as 1891 when the organism was isolated from a patient with pemphigus neonatorum [7]. Around 35% of the general population are commensal nasal carriers of *S. aureus* [8,9]. In neonates, *S. aureus* may also be isolated from the skin, eyes, umbilicus, perineum and wound sites [10]. Initial studies suggested that phage lytic group II *S. aureus* were mainly responsible for exfoliative toxin production, but it is now known that all phage groups are able to produce exfoliative toxin and cause SSSS [11,12]. Around 5% of all *S. aureus* produce exfoliative toxin [8,13,14] and two different serotypes affecting humans (ETA and ETB) have been identified [1,15]. In Europe, Africa and North America, ETA is more prevalent, accounting for more than 80% of exfoliative toxin-producing strains [13–18], whilst in Japan, ETB is more common [19]. Although they possess some physicochemical differences, ETA and ETB have 40% sequence homology and produce identical dermatological effects [20]. ETA consists of 242 amino acids, has a molecular mass of 26 950 kDa, is heat stable and the gene is

located in chromosomes, while ETB consists of 246 amino acids, has a molecular mass of 27 274 kDa, is heat labile and the gene is plasmid located [1,21].

A 27-kDa, thermolabile *S. aureus* exotoxin (termed ETC by the authors) that is serologically distinct from both ETA and ETB but able to produce mid-epidermal cleavage in newborn mice and chicks, has been isolated from a horse with a skin infection called phlegmon [22]. Similarly, three different exfoliative toxin serotypes, distinct from *S. aureus* exfoliative toxins, have been isolated from *S. hyicus* and shown to induce exudative epidermitis in young piglets – an infection characterized by exudation, exfoliation and vesicle formation in the epidermis [23]. These toxins are capable of causing exfoliation in newborn chicks but not in newborn mice; their role in human SSSS, if any, has not been determined.

Risk factors

A range of different interrelated host and organism factors govern the risk of developing SSSS. Infants and young children are particularly prone to generalized SSSS and two main theories have been proposed to explain this: protective antitoxin antibodies and renal function [1,2]. Immunosuppression has been shown in mice and humans to increase the risk of developing generalized SSSS [24], while maternal antibodies have been shown to protect newborns [25]. Epidemiological studies looking at antitoxin antibodies suggest that, in the localized form, *S. aureus* enters the skin through a break in the skin barrier (such as grazes, atopic dermatitis, or chickenpox) and produces the toxin locally, but hematogenous spread is limited by the presence of antitoxin antibodies [26]. In the generalized form, however, the toxin is usually produced at a distant site. This may be a colonization site (such as the nares, eye, umbilicus, groin, or wound site), or an infective site (such as pneumonia, osteomyelitis, or endocarditis) [27]. Lack of protective antibodies allows the toxin to spread through the bloodstream to reach the mid-epidermis via dermal capillaries to produce generalized exfoliation [26]. Work on radioactive labeled toxin in mice has shown that the toxin does not bind to any other organ in the body [28]. Renal function is also an important determinant in developing SSSS and may partly explain why young infants may be more susceptible. Adult mice can excrete up to one-third of a test dose of ETA within 3 h of injection compared to one-fifteenth in newborn mice [28]. Furthermore, nephrectomized adult mice are more likely to develop SSSS when administered ETA intravenously [28].

Toxin mechanism of action

Despite isolating and characterizing the toxins almost three decades ago, the mechanism by which they cause exfoliation has remained elusive. Initial studies using a range of different nonspecific substrates, including casein, showed no significant enzymatic activity, and exfoliation could not be prevented by a range of different metabolic inhibitors [1]. However, there is accumulating evidence that the toxins may act as atypical glutamate-specific serine proteases: (a) incubating ETA with neonatal mouse epidermis [29] or A431 epidermal cells [30] results in caseinolytic activity in the supernatant; (b) the toxins have significant sequence homology to V8 protease, another staphylococcal protein belonging to the trypsin-like serine proteases [31]; (c) modifying residue serine195 of the predicted serine protease active site of ETA results in loss of exfoliating activity in newborn mice [32,33]; (d) three-dimensional computer modeling of the toxins shows that their structure can be modeled on other glutamate-specific trypsin-like serine proteases, such as α-thrombin, chymotrypsin, *Streptomyces griseus* protease, and *Achromobacter* protease [34,35]; and (e) recent three-dimensional crystallographic images of both ETA and ETB show that the toxins consist of two domains, each made up of six antiparallel β-strands that form a β-barrel common to all members of the trypsin family, along with a serine protease catalytic triad of serine, histidine and aspartic acid [15,34,36]. In addition, the toxins possess Thr190 and His213 in the N-terminal pocket that are conserved in all glutamate-specific serine proteases. However, ETA differs from other serine proteases in that it possesses a large amphipathic N-terminal portion that covers the active site. This region may bind a specific epidermal receptor and cause a conformational change that opens the active site to induce serine protease activity. A similar mechanism has been proposed for other proteases, including thrombin and hepatitis C virus NS3 protease [36]. The structure of ETB is similar to ETA except that the oxyanion hole, which forms part of the catalytic site, is in the closed or inactive conformation for ETA, but in the open or active conformation for ETB [15]. Laboratory studies suggest that ETB may be more pyrogenic than ETA and enhances susceptibility to lethal shock in rabbits [37], while clinical studies have shown that, although both serotypes were equally responsible for localized SSSS, ETB was isolated more frequently from children with generalized SSSS (80% vs. 8% of 24 cases each) and may also be able to cause generalized exfoliation in apparently healthy adults [38].

Recently, Amagai's group demonstrated, using the newborn mouse model, that the clinical and histological features of SSSS and pemphigus foliaceus were almost identical [39]. In the latter condition, autoantibodies target desmoglein-1 to cause superficial blisters [40]. Desmoglein-1 is a desmosomal cadherin involved in intercellular adhesion and is found only in the superficial epidermis [41]. Disruption of this structure would result in loss of cell-to-cell adhesion and separation at the level of the zona granulosa. Amagai *et al.* also showed that incubating ETA with extracts of mouse epidermis resulted in cleaveage of

the 160 kDa desmoglein-1 protein, but not desmoglein-3 or epithelial cadherin, to a 113-kDa peptide [39]. ETA was also able to cleave the extracellular domain of mouse and human desmoglein-1 in a dose-dependent manner. The authors speculate that ETA acts as an atypical glutamate-specific serine protease that binds and cleaves desmoglein-1 in the region of amino acid number 170, where there are several glutamic acid residues [39]. This could explain several aspects of SSSS, including the specific site of action in the superficial epidermis and why the mucous membranes are not affected in SSSS, since desmoglein-1 is only found in the epidermis. Minor variations in the sequence or structure of desmoglein-1 may also explain the species specificity of SSSS [1].

However, the proposal that the exfoliative toxins cleave desmoglein-1 to produce exfoliation conflicts with several recent studies. For example, both exfoliative toxin serotypes cleave α- and β-melanocyte-stimulating hormones and this activity is not present with biologically inactive mutants of the toxins [42]. The authors suggest that these proteins may be the target for the toxins. On the other hand, a Japanese group isolated and purified a distinct 20 kDa protease from a supernatant of exfoliative toxin with neonatal mouse epidermis and showed that this protease could reproduce the mid-epidermal splitting of SSSS when injected subcutaneously into newborn mice [43].

Superantigenic activity

The debate as to whether the exfoliative toxins are superantigens continues and has been reviewed several times recently [34,37,44,45]. Initial work suggesting that the toxins were able to stimulate human Vβ2 and murine Vβ3 T cells [46,47,48] were refuted by studies suggesting that recombinant exfoliative toxin cloned into either non-toxin-producing *S. aureus* [49] or *Escherichia coli* [45] did not possess any superanitgenic activity, despite the recombinant toxin retaining its exfoliative activity. The authors suggest that the superantigenic activity in previous studies was probably due to contamination by other staphylococcal superantigens, such as toxic shock syndrome toxin-1 or the enterotoxins [45,49]. Vath *et al*. [34], however, showed that cloning ETA into a non-superantigenic strain of *S. aureus* resulted in superantigenic activity, and that recombinant ETA with a mutated active site (Ser195Cys) lost its exfoliative activity, but retained its mitogenic activity, suggesting that the mitogenic activity of the exfoliative toxin was separate from its exfoliative activity. ETA is also able to activate murine macrophages to release high levels of tumor necrosis factor-α, interleukin-6 and nitric oxide and cause contact-dependent cytotoxicity in transformed embryo fibroblast cells [50]. More recent work suggests that the exfoliative toxins may possess a unique and very specific superantigenic activity [37]. Using highly purified recombinant exfoliative toxins, Monday's group showed that, in the presence of antigen-presenting cells, both ETA and ETB were able to induce selective polyclonal expansion of several human Vβ-bearing T cells (but not Vβ2), and only those murine Vβ T cells that were highly homologous to the human forms. Although any superantigenic activity possessed by the exfoliative toxins is unlikely to play a major role in the pathogenesis of SSSS, it may be important in other diseases where superantigens are thought to be involved. Such conditions include acute exacerbations of atopic dermatitis, guttate and chronic plaque psoriasis, Kawasaki's disease, staphylococcal nephritis, staphylococcal septic arthritis, rheumatoid arthritis and other autoimmune diseases, and sudden infant death syndrome [1].

CLINICAL FEATURES

The clinical features of SSSS vary along a spectrum. The localized from is also known as bullous impetigo, bullous varicella and measles pemphigoid, and often presents with a few localized fragile superficial blisters filled with colorless to purulent fluid [51]. The surrounding skin appears normal and there are no systemic symptoms. In neonates, the lesions are often found around the umbilicus or the perineum, whilst in older children, they are more common on the extremities [17]. In the generalized form (also known as pemphigus neonatorum and Ritter's disease, after its original describer) patients often initially present with fever and erythema, with constitutional symptoms such as malaise, poor feeding and irritability, followed by large superficial blisters that quickly rupture, particularly in areas of friction [3]. Left untreated, large sheets of epidermis then slough off to leave extensive areas of raw denuded skin that is sensitive and painful (Figure 1). The condition may follow a localized staphylococcal infection, such as pneumonia, abscess, conjunctivitis, oomphalitis, septic arthritis, endocarditis or pyomyositis, but in most cases no focus is found [1,27]. A positive Nikolsky sign, which can be elicited by gentle rubbing of uninvolved or healed skin to produce dislodgement of the superficial epidermis, is characteristic of generalized SSSS, and mucous membranes are not affected [17,52].

The exfoliation of SSSS in itself rarely poses a problem since the level of epidermal cleavage is superficial, which means that scarring is rare (Figure 2). In infants and young children, potentially fatal complications of losing the protective epidermis include hypothermia, dehydration and secondary infections by organisms such as the pseudomonads [21,53]. With appropriate management, however, mortality due to SSSS in children remains below 5% [17,21,27]. On the other hand, generalized SSSS in adults carries a mortality rate of almost 60%, mainly because the majority of patients suffer from underlying conditions such as poor renal function, the use of immunosuppressive drugs, infections such as acquired immunodeficiency syndrome, and malignancy [27].

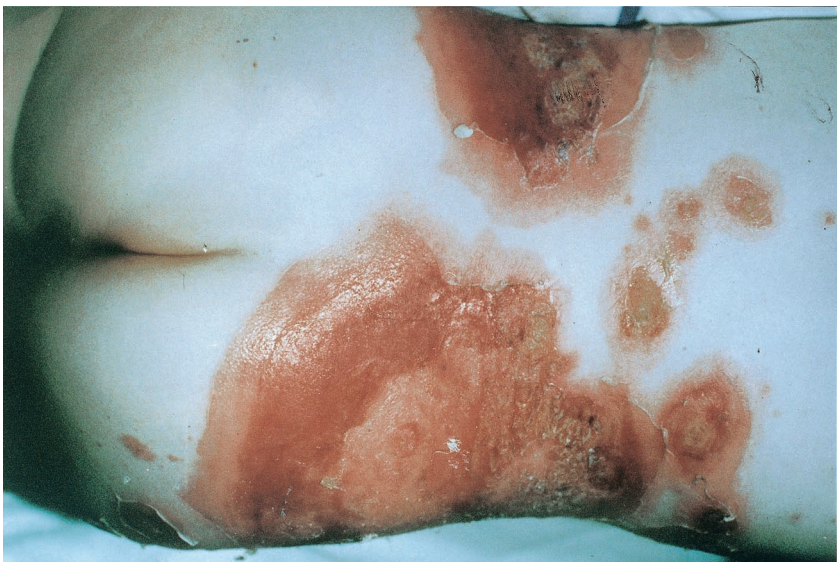

Figure1 Generalised SSSS in a 2-year-old child.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSES

Both the localized and generalized forms of SSSS are usually diagnosed by their characteristic clinical appearance, and differential diagnoses are few. It has been proposed that streptococcal impetigo can be distinguished from staphylococcal impetigo (localized SSSS) by its characteristic thick, dirty, golden crusting which soon reforms when removed [17,51]. However, this distinction is often difficult to make clinically, particularly since the two organisms can coexist. Few conditions resemble generalized SSSS when it presents in its extensive form. The main differential diagnosis remains erythema multiforme/toxic epidermal necrolysis, another exfoliating skin disorder that is more common in adults than children and carries a high mortality, particularly if not diagnosed early and managed appropriately [54]. It is caused by a variety of viral illnesses and drug reactions and can rapidly lead to multiorgan failure. Unlike SSSS, the mucous membrane is almost always affected, causing extensive erosions in the mouth, conjunctiva, trachea, bronchi, esophagus and genitalia [54]. Scalding and chemical burns must also be considered in the differential diagnosis for generalized SSSS, particularly in children, where neglect and non-

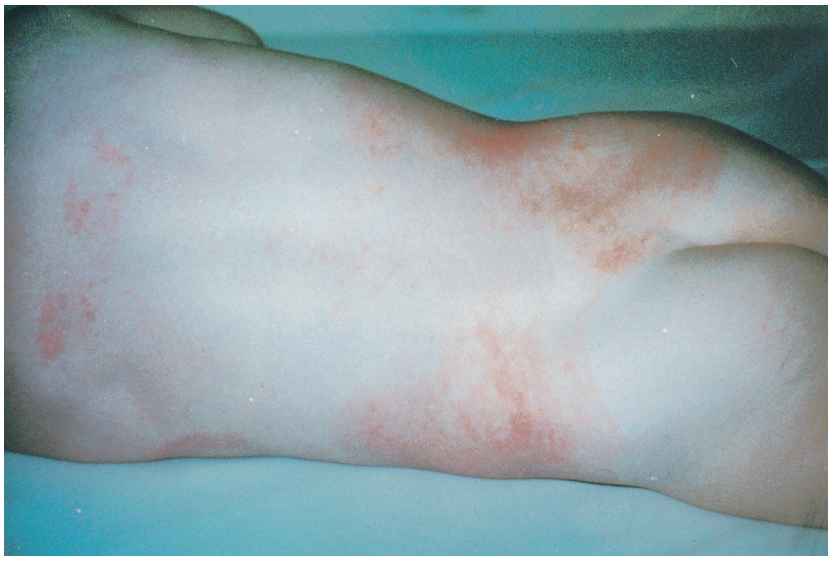

Figure 2 Same child 7 days after antibiotic therapy.

accidental injury may be suspected [51]. Other uncommon differential diagnoses include congenital disorders (epidermolysis bullosa, acrodermatitis enteropathica, bullous ichthyosis), other bacterial (staphylococcal superantigen-mediated conditions, streptococci and streptococcal scarlet fever, syphilis, listeriosis, *E. coli*, *Pseudomonas* and *Haemophilus* species) and viral (herpes, vaccinia, varicella zoster) infections, graft-versus-host reactions, diffuse cutaneous mastocytosis, Kawasaki disease and psoriasis [1,2].

INVESTIGATIONS

The difficulties in diagnosing SSSS have been reviewed recently [4]. A thorough examination is essential, not only to determine the extent of exfoliation but also to identify any potential focus of staphylococcal infection (such as pneumonia, an abscess, septic arthritis, endcarditis, etc.), the fluid status of the patient and any evidence of secondary skin infection. Superficial swabs of the lesions at the time of presentation are useful in both the localized and generalized forms of SSSS. The antibiotic sensitivity profile of *S. aureus* isolated may be useful in cases where empiric treatment is not successful, because of antibiotic resistance, for example [55]. In the generalized form, superficial swabs may also identify other organisms involved in secondary skin infection [53]. Exfoliative toxin-producing *S. aureus* may occasionally be isolated from blood cultures. This is more common in adults, who often have significant underlying disease and frank bacteremia; in children, blood cultures are usually negative because the toxins are produced at a distal site [27,56].

In cases where the diagnosis remains uncertain, the most useful investigation remains a skin biopsy, which is not practical in children [4]. In SSSS, the biopsy would show mid-epidermal splitting at the level of the zona granulosa, without cytolysis, cell necrosis or any inflammatory reaction [57]. Staphylococci may occasionally be seen in localized bullous lesions, but very rarely in generalized SSSS [58]. The biopsy is particularly useful in distinguishing SSSS from erythema multiforme/toxic epidermal necrolysis, where splitting occurs at the dermo-epidermal level [54,59].

A number of different laboratory investigations – including polymerase chain reaction (PCR), reverse passive latex agglutination, enzyme-linked immunosorbent assays and radioimmunoassays – have been developed to determine toxin production by *S. aureus* isolated from patients with suspected SSSS [60]. They are both sensitive and specific for the exfoliative toxins and most have been validated against the neonatal mouse model. However, they all rely on isolating *S. aureus* from the patient. We recently demonstrated that, of 72 *S. aureus* isolates from children with suspected generalized SSSS, only 35 (48.6%) produced exfoliative toxin when tested by PCR, suggesting that isolating *S. aureus* is neither sensitive nor specific (unpublished data). Hence, any further tests on the *S. aureus* strain isolated cannot be reliable. Also, given the time taken to culture and isolate the organism from peripheral and blood specimens, any further tests would only be useful for retrospective confirmation of the diagnosis [4]. Furthermore, *S. aureus* can be isolated from up to half the patients with toxic epidermal necrolysis and this can lead to a delay in correct diagnosis and inappropriate treatment [54]. We have recently developed a $F(ab')_2$ Fragment ELISA that can detect ETA not only from staphylococcal culture supernatants but also directly from serum with sensitivity in the picogram range. We are currently developing a similar ELISA-based detection system for ETB. If these diagnostic tests are successful in clinical studies, then diagnosis of SSSS could be confirmed within a few hours from routine blood tests [60].

TREATMENT

There is very little objective evidence for optimum treatment of SSSS [4]. Previous suggestions that antibiotics may not be useful in treating SSSS because the condition is toxin-mediated must be regarded with caution. Most clinicians will treat localized SSSS with oral antibiotics that cover both staphylococci and streptococci, and may add a topical agent since organisms may be present in the lesions. If generalized SSSS is diagnosed in its early stages, then oral antibiotics may be effective, with close observation. However, by the time the condition is diagnosed, the patient usually presents with widespread exfoliation. In such cases, intravenous antibiotics against penicillin-resistant *S. aureus* would be recommended. If there is any evidence of secondary skin infection, then an aminoglycoside should be added. Particular care must be given to pain management since the lesions are often very painful, and patients with severe peri-oral involvement may require short-term intravenous nutrition. Young infants require careful observation for dehydration, hypothermia and secondary infections. In severe cases of exfoliation, liaising with, and possibly transferring the patient to, the local burns unit may prove to be life-saving [61].

Because the condition is toxin-mediated, exfoliation usually continues 24–48 h after starting appropriate antibiotic treatment, although new lesions are uncommon after this period [3]. There have been several cases of methicillin-resistant *S. aureus* causing SSSS and this must be considered if the patient is not responding to empiric antibiotic treatment [55,62]. In most cases, the skin lesions heal rapidly over the next 7–10 days and, because the exfoliation is superficial, scarring is rare (Figure 2).

FUTURE TRENDS

Our understanding of SSSS has reached an exciting era. The recent identification of a specific substrate for the exfoliative toxins should speed up future research. How does the toxin get to desmoglein-1 in the mid-epidermis? Is there a specific

binding site for the toxin on desmoglein-1? Does the toxin act as an atypical protease as its structure suggests? Do ETB and other toxin homologs produced by *S. hycius* act in a similar fashion? Are minor changes in the desmoglein-1 protein related to susceptibility to SSSS? Understanding the mechanism of action of the toxins has direct clinical implications. The substrate could be used to develop more sensitive and specific diagnostic assays for SSSS. Analogs of desmoglien-1 could also be developed to inhibit the action of the toxins and therefore inhibit exfoliation. Previous work has shown that exfoliation can be halted or limited in mice given antitoxin antibodies early in the disease process [63]. Desmoglein-1 analogs could therefore be used to bind and neutralize the toxin *in vivo* and thereby prevent the toxin reaching the epidermis. Such therapy may become life-saving in SSSS cases of disseminated staphylococcal infection in immunocompromised patients [27] or when multiresistant *S. aureus* is responsible [55,62]. Similarly, having identified a very specific epidermal target, the toxins could be used in a controlled manner to induce localized exfoliation of offending superficial skin lesions with minimal scarring. The targeting and binding domain of the toxin could also be used to transport drugs to a very specific location within the epidermis with minimal systemic side-effects.

CONLUSIONS

Staphylococcal scalded skin syndrome is a relatively uncommon but potentially fatal disorder, particularly in adults who often have serious underlying disorders, and in young infants who are prone to secondary complications of exfoliation. Clinicians should maintain a high index of suspicion in all cases of superficial exfoliating disorders in both children and adults, particularly when associated with symptoms or signs of infection. The past few years have seen a remarkable development in our understanding of the condition. The three-dimensional structure of the exfoliative toxins has been elucidated, their specific epidermal substrate identified and a unique superantigenic activity proposed. In the clinical arena, there have been several reports of methicillin-resistant *S. aureus* causing SSSS, and detection systems have been developed to diagnose the condition rapidly. However, although these recent breakthroughs have been a major step forward, they have opened a whole new area for further research. In particular, it is hoped that the identification of the substrate will lead to new antitoxin strategies to prevent exfoliation in the near future.

REFERENCES

1. Ladhani S, Joannou CL, Lochrie DP, Evans RW, Poston SM. Clinical, microbial and biochemical aspects of the exfoliative toxins causing staphylococcal scalded skin syndrome. *Clin Microbiol Rev* 1999; 12: 224–42.
2. Ladhani S, Evans RW. Staphylococcal scalded skin syndrome. *Arch Dis Child* 1998; 78: 85–8.
3. Ladhani S, Newson T. A familial outbreak of staphylococcal scalded skin syndrome. *Pediatr Infect Dis J* 2000; 19: 578–9.
4. Ladhani S, Joannou CL. Difficulties in the diagnosis and management of staphylococcal scalded skin syndrome. *Pediatr Infect Dis J* 2000; 142: 1251–5.
5. von Rittershain GR. Die exfolitive dermatitis jungener senglinge. *Z Kinderheilkd* 1878; 2: 3–23.
6. Melish ME, Glasgow LA. The staphylococcal scalded skin syndrome: development of an experimental model. *N Engl J Med* 1970; 282: 1114–9.
7. Almquist E. Pemphigus neonatorum, backteriologisch und epidemiologisch beleuchtet. *Z Hyg Infectionskr* 1891; 10: 253.
8. Dancer SJ, Noble WC. Nasal, axillary and perineal carriage of *Staphylococus aureus* among pregnant women: identification of strains producing epidermolytic toxin. *J Clin Pathol* 1991; 44: 681–4.
9. Noble WC. *The Micrococci*. London: Lloyd-Luke, 1981; 152–81.
10. Dancer SJ, Simmons NA, Poston SM, Noble WC. Outbreak of staphylococcal scalded skin syndrome among neonates. *J Infect* 1988; 16: 87–103.
11. Dajani AS. The scalded skin syndrome: relation to phage group II staphylococci. *J Infect Dis* 1972; 125: 548.
12. Kondo I, Sakurai S, Sarai Y. New type of exfoliatin obtained from staphylococcal strains belonging to phage group other than group II, isolated from patients with impetigo and Ritter's disease. *Infect Immun* 1974; 10: 851–61.
13. 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.
14. Elsner P, Hartman AA. Epidemiology of ETA- and ETB-producing staphylococci in dermatological patients. *Zentbl Bacteriol Mikrobiol Hyg Series A* 1988; 268: 534.
15. Papageorgiou AC, Plano LR, Collins CM, Acharya KR. Structural similarities and differences in *Staphylococcus aureus* exfoliative toxins A and B as revealed by their crystal structure. *Protein Sci* 2000; 9: 610–8.
16. De Azavedo A, Arbuthnott JP. Prevalence of epidermolytic toxin in clinical isolates of *Staphylococcus aureus*. *J Med Microbiol* 1981; 14: 341–4.
17. Melish ME. Staphylococci, streptococci and the skin: review of impetigo and staphylococcal scalded skin syndrome. *Semin Dermatol* 1982; 1: 101–9.
18. Piemont Y, Monteil H. New approach in the separation of two exfoliative toxins from *Staphylococcus aureus*. *FEMS Microbiol Lett* 1983; 17: 191–5.
19. Kondo I, Sakurai S, Sarai Y, Fukati S. Two serotypes of exfoliatin and their distribution in staphylococcal strains isolated from patients with scalded skin syndrome. *J Clin Microbiol* 1975; 1: 397–400.
20. Bailey CJ, de Azavedo JJ, Arbuthnott JP. A comparative study of two serotypes of epidermolytic toxins from *Staphylococcus aureus*. *Biochim Biophys Acta* 1980; 624: 111–20.
21. Gemmell CG. Staphylococcal scalded skin syndrome. *J Med Microbiol* 1997; 43: 318–27.
22. Sato H, Matsumori Y, Tanabe T *et al*. A new type of staphylococcal exfoliative toxin isolated from a *Staphylococcus aureus* strain isolated from a horse phlegmon. *Infect Immun* 1994; 62: 3780–5.
23. Anderson LO. Differentiation and distribution of three types of exfoliative toxin produced by *Staphylococcus hyicus* from pigs with exudative epidermitis. *FEMS Immunol Med Microbiol* 1998; 20: 301–10.

24. Wiley BB, Allman S, Rogolsky M, Norden CW, Glasgow LA. Staphylococcal scalded skin syndrome: potentiation by immunosuppression in mice: toxin-mediated exfoliation in a healthy adult. *Infect Immun* 1974; 9: 636–40.
25. Machida K. Immunological investigations on the pathogenesis of staphylococcal scalded skin syndrome. *J Clin Pathol* 1995; 43: 547–56.
26. Melish ME, Chen FS, Sprouse S, Stuckey M, Murata MS. Epidermolytic toxin staphylococcal infection: toxin levels and host response. In: Jeljaszewicz J, ed. *Staphylococci and Staphylococcal Infections*. Stuttgart: Gustav Fischer-Verlag, 1981; 287–98.
27. Cribier B, Piemont Y, Grosshans E. Staphylococcal scalded skin syndrome in adults: a clinical review illustrated with a case. *J Am Acad Dermatol* 1984; 30: 319–24.
28. Fritsch P, Elias P, Varga J. The fate of staphylococcal exfoliatin in newborn and adult mice. *Br J Dermatol* 1976; 95: 275–84.
29. Takiuchi I, Kawamura I, Teramoto T, Higuchi D. Staphylococcal exfoliative toxin induces caseinolytic activity. *J Infect Dis* 1987; 156: 508–9.
30. Ladhani S, Joannou CL, Poston SM, Evans RW. Staphylococcal scalded skin syndrome: exfoliative toxin A induces serine protease activity when combined with A431 cells. *Acta Paediatr* 1999; 88: 776–9.
31. Dancer SJ, Garratt R, Saldanha J, Jhoti H, Evans R. The epidermolytic toxins are serine proteases. *FEBS Lett* 1990; 268: 129–32.
32. Prevost G, Rifai S, Chaix L, Piemont Y. Functional evidence that the Ser-195 residue of staphylococcal exfoliative toxin is essential for biological activity. *Infect Immun* 1991; 59: 3337–9.
33. 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.
34. Vath GM, Earhart CA, Rago JV *et al*. The structure of the superantigen exfoliative toxin A suggests novel regulation as a serine protease. *Biochemistry* 1997; 36: 1559–66.
35. 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 Eng* 1996; 9: 591–601.
36. Caverelli J, Prevost G, Bourguet W *et al*. The structure of *Staphylococcus aureus* epidermolytic toxin A, an atypic serine protease, at 1.7A resolution. *Structure* 1997; 5: 813–24.
37. Monday SR, Vath GM, Ferens WA *et al*. Unique superantigen activity of staphylococcal exfoliative toxins. *J Immunol* 1999; 162: 4550–9.
38. Opal SM, Johnson-Winegar AD, Cross AS. Staphylococcal scalded skin syndrome in two immunocompetent adults caused by exfliatin B-producing *Staphylococcus aureus*. *J Clin Microbiol* 1988; 26: 1283–6.
39. Amagai M, Matsuyosih N, Wang ZH, Andl C, Stanley JR. Toxin in bullous impetigo and staphylococcal scalded–skin syndrome targets desmoglein-1. *Nat Med* 2000; 6: 1275–7.
40. Koulu L, Kusumi A, Steinberg MS, Klaus-Kovttin V, Stanley JR. Human autoantibodies against a desmosomal core protein in pemphigus foliaceus. *J Exp Med* 1984; 160: 1509–18.
41. Mahoney MG, Wang Z, Rothenberger K, Koch PJ, Amagai M, Stanley JR. Explanation for the clinical and microscopic localization of lesions in pemphigus foliaceus and vulgaris. *J Clin Invest* 1999; 103: 461–8.
42. Rago JV, Vath GM, Tripp TJ, Bohach GA, Ohlendorf DH, Schlievert PM. Staphylococcal exfoliative toxins cleave alpha- and beta-melanocyte stimulating hormones. *Infect Immun* 2000; 68: 2366–8.
43. Ninomiya J, Ito Y, Takiuchi J. Purification of a protease from a mixture of exfoliative toxin and newborn-mouse epidermis. *Infect Immun* 2000; 68: 5044–9.
44. Bailey CJ, Lochart BP, Redpath MB, Smith TP. The epidermolytic (exfoliative) toxins of *Staphylococcus aureus*. *Med Microbiol Immunol* 1995; 184: 53–61.
45. Plano LRW, Gutman DM, Woischnik M, Collins CM. Recombinant *Staphylococcus aureus* exfoliative toxins are not bacterial superantigens. *Infect Immun* 2000; 68: 3048–52.
46. Morlock BA, Spero L, Johnson AD. Mitogenic activity of staphylococcal exfoliative toxin. *Infect Immun* 1980; 30: 381–4.
47. Choi Y, Kotzin B, Herron L, Callahan J, Marrack P, Kappler J. Interaction of *Staphylococcus aureus* toxin superantigens with human T cells. *Proc Natl Acad Sci USA* 1990; 86: 8941–5.
48. Herman A, Croteau G, Sekaley RP, Kappler J, Marrack P. HLA-DR alleles differ in their ability to present staphylococcal enterotoxins to T cells. *J Exp Med* 1990; 172: 709–17.
49. Fleischer B, Bailey CJ. Recombinant epidermolytic (exfoliative) toxin A of *Staphylococcus aureus* is not a superantigen. *Med Microbiol Immunol* 1992; 180: 273–8.
50. Fleming SD, Iandolo JJ, Chapes SK. Murine macrophage activation by staphylococcal exotoxins. *Infect Immun* 1991; 59: 4049–55.
51. Lyell A. Toxic epidermal necrolysis (the scalded skin syndrome): a reappraisal. *Br J Dermatol* 1979; 100: 69–86.
52. Moss C, Gupta E. The Nikolsky sign in staphylococcal scalded skin syndrome. *Arch Dis Child* 1998; 79: 290.
53. Hoffmann RR, Lohner M, Bohm N, Schaefer HE, Letitis J. Staphylococcal scalded skin syndrome and consecutive septicaemia in a preterm infant. *Pathol Res Pract* 1994; 190: 77–81.
54. Revuz J, Penso D, Roujeau JC *et al*. Toxic epidermal necrolysis: clinical findings and prognostic factors in 87 patients. *Arch Dermatol* 1987; 123: 1166–70.
55. Yokota S, Imagawa T, Kataakura S, Mitsuda T, Arai T. Staphylococcal scalded skin syndrome caused by exfoliative toxin B-producing methicillin-resistant *Staphylococcus aureus*. *Eur J Pediatr* 1996; 155: 722.
56. Goldberg NS, Ahmed T, Robinson B, Ascensao H, Horwitz H. Staphylococcal scalded skin syndrome mimicking acute graft-versus-host disease in a bone marrow transplant recipient. *Arch Dermatol* 1989; 15: 385–9.
57. Gentilhomme E, Faure M, Piemont Y, Binder P, Thivolet J. Action of staphylococcal exfoliative toxins on epidermal cell cultures and organotypic skin. *J Dermatol* 1990; 17: 526–32.
58. Beers B, Wilson B. Adult staphylococcal scalded skin syndrome. *Int J Dermatol* 1990; 29: 428.
59. Feldman SR. Bullous dermatoses associated with systemic disease. *Dermatol Clin* 1993; 11: 597–609.
60. Ladhani S, Robbie S, Garratt RC *et al*. Development and evaluation of detection systems for staphylococcal exfoliative toxin A responsible for the scalded skin syndrome. *J Clin Microbiol* 2001; 39: 2050–2054.
61. Greenwood JE, Dunn KW, Davenport PJ. Experience with severe blistering skin disease in a paediatric burns unit. *Burns* 2000; 26: 82–7.
62. Ackland KM, Darvay A, Griffin C, Aali SA, Russell-Jones R. Staphylococcal scalded skin syndrome in an adult associated with methicillin-resistant *Staphylococcus aureus*. *Br J Dermatol* 1999; 14: 518–20.
63. Kapral FA. *Staphylococcus aureus*: some host–parasite interactions. *Ann NY Acad Sci* 1974; 236: 267–75.