Staphylococcal scalded skin syndrome

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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. Current synonyms include Ritter’s disease, bullous impetigo, pemphigus neonatorum, and staphylococcal scarlatiniform rash. It is a disease primarily affecting infants and young children, but cases have been reported in adults. 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. 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. 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. Antibiotic treatment with β-lactamase resistant semisynthetic penicillins such as flucloxacillin is usually effective. 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.

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 and over 50% in adults, reaching almost 100% in those with underlying disease (see below), despite antibiotic treatment.

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.

The toxins
The role of the exfoliative toxins in SSSS was demonstrated as far back as 1970, 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, 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, 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. The toxins in their native form, however, do not have any significant proteolytic activity, 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 proteases; (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; (3) incubation of ETA with neonatal mouse epidermis or neonatal mouse epidermal extract results in the induction of caseinolytic activity in the supernatant; and (4) recent computer modelling and crystallographic studies 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, 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.
Epidemiology

*Staphylococcus aureus* is a Gram positive coccus which colonises the nose, perineum, axillae, eyes, wound sites, and toe webs. Two toxin serotypes are known—ETA and ETB—but others may exist. In contrast, in Japan nasal carriers of babies discharged from the hospitals may be screened, and 6.2% of 2362 isolates from hospital patients, 3% of isolates from 500 antenatal women, and 4.0% of isolates from various clinical sources in Nigeria. Hargiss and Larson found that up to 60% of newborn babies discharged from the hospitals may be nasal carriers of *S aureus*. 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. 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, 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, 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. 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. 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. 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. 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. 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
necrolysis, burns, epidermolysis bullosa, bul-
rous erythema multiforme, listeria and syphilis
infections, diffuse cutaneous mastocytosis, and
graft versus host reaction. 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 exam-
ple, simple epidemiological data on SSSS, such
as age distribution, sex ratio, ethnic suscepti-
bilities, 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 condi-
tions such as eczema and sudden infant death
syndrome.

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 sub-
stantiated 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 newborn or
hairless 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 sur-
gery, keratinocyte cultures, and mouse epider-
mis have been used to demonstrate epidermal
splitting at the zona granulosa. All these
assays are difficult to perform and replicate,
thus hampering research.

However, research using the neonatal mouse
epidermis assay could be extended to inves-
tigate whether the exfoliative toxins are indeed
serine proteases and whether they bind to any
receptors, and to elucidate events following
binding. The model could also be used to
determine any changes occurring in ETA,
including a conformational change after recep-
tor binding to expose the active catalytic site, as
has recently been speculated from structural
models. The main difficulty is the use of
mouse epidermis, but keratinocytes cell cul-
tures, 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 pseudo-
monas exotoxin A, have already served a
similar purpose and provided novel treatments
for various carcinogenic, immunological, and
haematological disorders. Furthermore, if anti-
toxin 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 superfi-
cial 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 dis-
ease, where mortality rates are high.

Conclusions

Although SSSS is relatively uncommon, usu-
ally 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, out-
breaks are difficult to control, and the second-
ary complications, which are particularly com-
mon in neonates, can often be lethal.

Furthermore, clinicians should be aware of
three recently emerging trends. Firstly, al-
though phage group II staphylococci only
rarely develop antibiotic resistance, one
such case has already been described recently,
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, 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.

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. While indi-
vidual 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 SSIS 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. SSS 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.

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