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Review Article **Open Access**

A review of staphylococcal scalded skin syndrome

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Abstract:

Staphylococcal scalded skin syndrome (SSSS) is characterized by widespread epithelial necrosis and/or superficial blistering of the skin following infection by some toxigenic strains of *Staphylococcus aureus*. The disease primarily affects children under the age of 5 years, but it can also occur in adults. Due to the recent increase in reported cases of SSSS, we have reviewed the epidemiology, pathogenesis, clinical features, diagnosis, treatment, and prevention, including the development of vaccines for *S. aureus* infections. Electronic databases including PubMed, Google Scholar and websites of the Center for Disease Prevention and Control (CDC), and the World Health Organization (WHO), were searched for publications on SSSS written in English language. Our review showed that SSSS is more common in children, amongst whom it carries a mortality rate of <5%, as opposed to mortality rate of >50% in affected adults. Penicillinase-resistant penicillins are recommended for the treatment of SSSS, and administration of fresh frozen plasma (FFP) may aid early recovery. Important staphylococcal vaccine candidates are also highlighted in the review.

Keywords: staphylococcal scalded skin syndrome, staphylococcal skin infection, staphylococcal vaccines

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Un examen du syndrome de la peau échaudée staphylococcique

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Résumé:

Le syndrome de la peau échaudée staphylococcique (SSSS) est caractérisé par une nécrose épithéliale généralisée et/ou des cloques superficielles de la peau suite à une infection par certaines souches toxigènes de *Staphylococcus aureus*. La maladie touche principalement les enfants de moins de 5 ans, mais elle peut également survenir chez les adultes. En raison de l'augmentation récente des cas signalés de SSSS, nous avons examiné l'épidémiologie, la pathogenèse, les caractéristiques cliniques, le diagnostic, le traitement et la prévention, y compris le développement de vaccins contre les infections à *S. aureus.* Des bases de données électroniques, notamment PubMed, Google Scholar et les sites Web du Centre de Prévention et de Contrôle des Maladies (CDC) et de l'Organisation Mondiale de la Santé (OMS), ont été recherchées pour des publications sur SSSS rédigées en anglais. Notre revue a montré que le SSSS est plus fréquent chez les enfants, parmi lesquels il entraîne un taux de mortalité < 5%, par opposition à un taux de mortalité > 50% chez les adultes affectés. Les pénicillines résistantes à la pénicillinase sont recommandées pour le traitement du SSSS, et l'administration de plasma frais congelé (PFC) peut favoriser une récupération précoce. D'importants candidats vaccins staphylococciques sont également mis en évidence dans l'examen.

Mots-clés: syndrome de la peau échaudée staphylococcique, infection cutanée staphylococcique, vaccins staphylococciques

Introduction:

Staphylococcal scalded skin syndrome (SSSS) is a rare but severe skin infection caused by the exfoliative toxins produced by the bacterium *Staphylococcus aureus.* The disease, also known as Ritter's disease, is named after Gotfried Ritter who published case series of about 300 patients with SSSS in the 1800s (1,2). *Staphylococcus aureus* is a significant cause of serious bacterial infections especially sepsis where it is commonly reported (3,4). It is a significant public health concern due to its potential to cause significant morbidity and mortality, especially in infants and in immunocompromised individuals. The syndrome is characterized by a spectrum of diffuse erythematous rash and skin peeling, which can lead to life-threatening complications (5). It primarily affects children under the age of 5 years, but can also occur in adults (5-10).

The pathogenesis of SSSS is complex and involves the breakdown of desmoglein-1 present in the outer layer of the skin by the exfoliative toxins produced by *S. aureus* (11). This results in the detachment of the top layer of the skin, causing the characteristic blistering and peeling seen in SSSS (1,9-12). Diagnosis of SSSS is challenging and requires a high degree of clinical suspicion as the early stages of the disease can be easily mistaken for other common childhood illnesses such as pemphigus vulgaris and Stevens-Johnson syndrome. Treatment typically involves supportive care, wound management, and antibiotics targeting the underlying *S. aureus* infection (13).

In recent years, there has been an increasing interest in developing effective prevention strategies for SSSS, including the development of vaccines against *S. aureus* infections (1,2,14,15). Despite these efforts, there are still many unanswered questions regarding the pathogenesis, diagnosis, and management of SSSS. This review aims to provide a comprehensive overview of the current aspects of SSSS, including its epidemiology, pathogenesis, clinical features, diagnosis, treatment, and prevention. Additionally, we discuss the current state of research on SSSS, including the development of vaccines for *S. aureus* infections. By consolidating the available knowledge on SSSS, we hope that this review will serve as a valuable resource for clinicians, researchers, and public health professionals working towards better understanding and management of SSSS.

Methodology and Results:

Electronic databases including PubMed and Google Scholar were searched to identify publications on SSSS. Other online sources searched included the Center for Disease Prevention and Control (CDC), and World Health Organization (WHO) websites, as well as grey literatures. The keywords used for the search were "staphylococcal scalded skin syndrome" and "staphylococcal skin infection" and the search period was from January 1, 2010 to December 31, 2022.

Inclusion criteria were original and review publications that provided information on SSSS in humans, case reports of SSSS, epidemiology and genomic sequences of *S. aureus* implicated in scalded skin syndrome (SSS), pathophysiology, and management of SSSS. Publications written in any language other than English, letters to the editors and animal reports were excluded. All duplicate publications were removed, and the full text of selected articles were reviewed by the authors for eligibility, with areas of conflict sorted out by consensus among the authors. A total of seventy publications were finally included for the review.

Discussion:

Epidemiology of SSSS

The incidence of SSSS varies across different geographic regions, but it is estimated to be less than one case per million people per year in most developed countries (5,16-18). The incidence of SSSS may be higher in developing countries due to poor hygiene and living conditions (1,2). SSSS is more common in warmer climates and is more frequently reported during the summer months. SSSS primarily affects children under the age of 5 years, with a peak incidence in infants less than 2 years old (1,2). There is an inverse relationship with age (16,19). SSSS is reported to be more common in males than females, with a male to female ratio of approximately 2:1.

The risk factors for SSSS include underlying skin infections, such as impetigo, and conditions that compromise the immune system such as HIV/AIDS, chemotherapy, or long-term use of immunosuppressive medications (14,16,20-23). Individuals who are colonized with *S. aureus*, but not necessarily infected, are also at an increased risk for developing SSSS (23-25). Newborns and infants are particularly vulnerable to *S. aureus* colonization due to the immaturity of their immune systems and the increased permeability of their skin (2,26). The proportion of individuals who develop SSSS is much lower than those harbouring *S. aureus* primarily because only about 2-5% of *S. aureus* harbour the epidermolytic/exfoliative toxin (ET) *eta* or *etb* genes (27,28).

Outbreaks of SSSS have been reported in neonatal intensive care units and other

hospital settings (5,29). The disease can be spread from person to person through direct contact or by fomites, such as towels or clothing contaminated with *S. aureus* (5,30). Therefore, infection control measures, such as hand hygiene and proper disinfection of equipment and surfaces, are essential to prevent the transmission of *S. aureus* and consequent SSSS in healthcare settings.

Although SSSS is rare, it can be life-threatening and has a significant impact on affected individuals and their families (5,18, 30). It is crucial to maintain a heightened level of awareness and implement effective measures to prevent and manage SSSS, particularly in populations with a higher susceptibility. Such measures should include the adoption of proper wound care practices, timely treatment of any underlying skin infections, and the use of antibiotics to specifically target the underlying *S. aureus* infection. Vaccines against *S. aureus* infections are currently under development and may offer future promise in preventing SSSS (15).

Aetiology of SSSS:

There are three serological forms of staphylococcal ETs (ETA, ETB, and ETD), all of which cleave human desmoglein (31) but only ETA and ETB have been firmly linked to human SSSS (32). In a review, Ladhani et al., (26) suggested that ETB is more frequently isolated than ETA in children with generalized SSSS. The ET comprises of two proteins; ET-A (chromosomal, heat stable) and ET-B (plasmid encoded, heat labile), which act specifically on the zona granulosa of the skin epidermis (33).

Immunocytochemical studies have demonstrated that the toxin binds to the filaggrin group of proteins in keratohyalin granules (34). Most strains of *S. aureus* isolated from patients with an occult or overt infection or colonization with ET–secreting *S. aureus* belong to phage group II and the most common subtypes are 3A, 3B, 3C, 55 and 71 (23). Exotoxin secretion occurs during the bacterial logarithmic growth phase (35).

Risk factors for SSSS:

A suppressed immune system, whether from renal failure, diabetes mellitus (DM) or human immunodeficiency virus (HIV) infection, results in inability to both excrete *S. aureus* exotoxins and to produce antibodies to the ETs (16). Patients undergoing haemodialysis are at risk of SSSS due to infection by *S. aureus* via vascular access port, inability to excrete ETs, and the immunological deficits that accompany renal failure (36,37). In cases of adults without immunosuppression who developed SSSS, it is likely that they contracted strains of *S. aureus* with *etb* gene which encodes virulent exotoxin ETB (38).

Pathogenesis of SSSS:

The pathogenesis of SSSS is complex and involves a number of factors that contribute to the development of the disease with the clinical features being mediated by *S. aureus* ETs. It is estimated that only about 2-5% of all *S. aureus* strains produce ETs (27, 28). ETs are a class of serine protease exotoxins of two major distinct types; ETA and ETB. They are also referred to as epidermolytic toxins, epidermolysins, and exfoliatins (39). These toxins are heat-stable and resistant to proteases and acidic pH, allowing them to survive in harsh environments and cause damage to the skin. The exfoliative toxins C (ETC) and D (ETD) are isoforms which have been observed in other animal models.

The ETA and ETB are encoded by genes carried on *S. aureus* bacteriophage and plasmid respectively (40). These toxin genes can integrate into the bacterial chromosome and transfer the genes between bacteria. The toxin is released following expression of the genes locally by staphylococci, which travels through the body, and then concentrates at the stratum granulosum layer (26,28,39). The toxins are produced during the post-exponential phase of bacterial growth as inactive precursor molecules, which are then activated by proteolytic cleavage by *S. aureus* proteases such as aureolysin and staphopain A.

Once activated, the toxins bind to and cleave the desmoglein 1 (Dsg1) protein. The Dsg1 protein is the primary component responsible for the maintenance of interkeratinocyte adhesion desmosomes that maintain skin cell integrity. The cleavage of Dsg1 thus leads to the detachment of the top layer of the skin, resulting in the characteristic blistering and peeling seen in SSSS. Although the toxins act by a direct effect on the stratum granulosum of the epidermis, the mucosa is never involved (39,41). The toxins ETA and ETB have different mechanisms of action in causing SSSS. ETA is a single-chain toxin that directly cleaves Dsg1 within the skin, while ETB is a two-component toxin that binds to Dsg1 on the surface of skin cells and then triggers cleavage by host proteases (12,32,40,42). Both toxins can cause significant damage to the skin and lead to the formation of blisters, bullae, and exfoliation of the skin.

The severity of SSSS is influenced by various factors, including the amount and type of ETs produced, the patient's immune response, and the patient's age and overall health (11). Infants and young children are more susceptible to SSSS due to their immature immune systems and thinner skin, which is more easily damaged by the ETs (43,44). Immunocompromised individuals such as HIV/AIDS, cancer, or those undergoing chemotherapy, are also at increased risk of developing

severe SSSS (20). It has been postulated that ET targets Dsg1 in the vicinity of the cell membrane ganglioside (GM4), which is mostly ever present in the skin of young children or in adults with peculiar skin diseases (45,46).

Clinical features of SSSS:

The clinical features of SSSS are characterized by a wide spectrum of diffuse erythematous rash and skin peeling, which can lead to life-threatening complications (23,45). The spectrum includes, the localized and the generalized which represent the two broad ends of the observed spectrum. In general, the disease typically begins with the development of a fever, followed by the appearance of a red rash on the skin, which spreads rapidly throughout the body (14,46). The rash is usually accompanied by pain, tenderness, and blistering of the affected area. The characteristic feature of SSSS is the presence of skin peeling, which can occur within hours of the onset of the rash. The skin peeling typically begins around the mouth and eyes, and then spreads to the rest of the body, including the trunk and extremities (23,46). The skin peeling usually begins as small blisters, which then rupture and leave behind raw, denuded skin. The affected skin may appear shiny, red, and moist, and may be tender to the touch. The skin easily detaches by mere rubbing, which is described as Nikolsky's sign (23).

Bullous impetigo, also known as the localized form of SSSS, can occur when the toxin spreads locally around a previously colonized wound in individuals who possess some immunity to the toxin (23,24). This type of impetigo is frequently observed in neonates around the umbilicus, in infants who still have maternal immunity, or in older people who have already have some form of immunity. Although antibodies hinder the distant dissemination of the toxin, they do not prevent its local spread in the colonized or infected region (31,44). Unlike the generalized form, bullous impetigo is confined to a specific area and the blister fluid may contain bacteria and, in some cases, white blood cells (38).

In severe cases of SSSS, the skin peeling can be so extensive that large areas of the body are left with raw, exposed skin. This highly increase the risk of secondary bacterial infections, as well as dehydration and electrolyte imbalances (39,43). Other potential complications of SSSS include sepsis, pneumonia, and kidney failure. The disease is self-limited and wanes within 4 to 5 days in children, which probably parallels the appearance of specific antitoxin immunoglobulins (47,48).

Diagnosis of SSSS:

The diagnosis of SSSS can be challenging, as the early stages of the disease may be easily mistaken for other common childhood illnesses. However, the presence of fever, diffuse erythematous rash, and skin peeling can help to differentiate SSSS from other conditions (14,46). In addition, laboratory investigations, such as blood cultures and skin biopsies, can aid in confirmatory diagnosis and identification of the underlying *S. aureus* infection.

Treatment and prognosis of SSSS:

Patient with SSSS should be promptly isolated, and those at risk of developing SSSS and who may have been exposed to ET-producing *S. aureus* strains will benefit from prompt administration of prophylactic anti-staphylococcal antibiotics (14,26,31). It is important to start empirical antibiotics as early as possible, and penicillinase-resistant penicillins are recommended, as they are effective in treatment of methicillin-sensitive *S. aureus* infection seen in most patients with SSSS (49-51). If the patient has a penicillin allergy, clarithromycin or cefuroxime may be used as alternative. It is still debatable as to whether antibiotics delivered intravenously have superior efficacy than oral administration (52). If a patient is not improving, it is necessary to consider ETs produced by methicillin-resistant *S. aureus* and switch antibiotic to vancomycin (53).

It has been observed that more than 90% of adults above 40 years of age have antibodies against ETA. Therefore, children with SSSS may receive a dose of fresh frozen plasma (FFP) (10 ml/kg) to neutralize exotoxin (54). If appropriately managed, the prognosis of SSSS in children is usually good, with mortality rate less than 5%. In contrast, the mortality rate can be very high in adults (>50%), which is usually associated with an underlying medical condition (14,23).

Prevention of SSSS and efforts at vaccine development:

SSSS can be prevented by adhering to good hygiene practices which include proper and frequent hand hygiene with antibacterial hand soap and observing hand hygiene moments; avoid sharing items such as towels and clothes; keeping fingernails short and clean; using clean and dry beddings and clothing; keeping wounds and cuts clean and covered; preventing contact of infected individuals with child care centers and schools; staphylococcal decolonization with antibacterial creams such as fusidic acid or petroleum jelly under fingernails, and environmental cleaning with antibacterial agents (36,55).

Currently, there are no vaccines available against *S. aureus* although numerous attempts have been made to develop effective vaccines that would activate both humoral and cellular immunity against *S. aureus* infections (56,57). Significant limitations have been ob-

served in translation of vaccine protectivity from preclinical phases to the clinical phase. In addition to vaccines, other novel strategies are being developed in the management of *S. aureus* infections before an efficacious vaccine is available and these include the use of monoclonal antibodies, bacteriophage therapy, antibiotics, and development of new therapeutic proteins such as centyrins (15).

The various techniques that have been employed in the development of *S. aureus* vaccines include the use of recombinant protein or bacterial polysaccharide antigen. This is the most common technique employed as it has been successful in the development of vaccines for other bacterial infections such as *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae* B (HiB). The use of protein glycol-conjugation is employed to stimulate T-cell dependent B-cell activation and immune response to polysaccharide antigens, which is strong and long-lived (58).

Another technique includes the use of extracellular vesicles (EV) by genetically modifying *S. aureus* using *Escherichia coli* transfected with plasmids encoding five staphylococcal antigens, which are subsequently trafficked into the outer membrane vesicles (OMVs) that are naturally found in Gram-negative bacteria, in order to stimulate the innate and adaptive immune systems (59). Recently, *S. aureus* was also found to secrete extracellular vesicles which have inherent adjuvant ability useful for stimulating innate pro-inflammatory cytokines such as IL-6, IL-12 and TNF-α by dendritic cells (DCs) and dermal fibroblasts in the host, which is therefore being explored as a vaccination technique (60-62). The EVs of *S. aureus* have been proven to stimulate long-lived immunity against subsequent infections through T-cell derived IFN-γ (61,63,64).

The use of whole cell and live attenuated bacteria has also been explored by either physically or chemically inactivating bacteria or using live attenuated bacteria. Recently, an attenuated auxotrophic mutant of MRSA strain 132 was developed which was found to provide high immunogenic protection and produced cross-reactive antibodies against *S. aureus* strains in mice (65). A number of whole cell vaccines have successfully passed the preclinical stages in both mice, bovine and human models. Two whole cell *S. aureus* vaccines, Startvac and Lysigin, were approved for use in mice, while chloroform inactivated *S. aureus* (SA75) and heat-killed (HK) *S. aureus* strain ATCC 12598 passed early phase clinical trials in humans. However, there are limited data on these vaccines in humans as they were not developed further (66,67) possibly because manufacturers prefer to use newer technologies or because whole cell and live attenuated vaccines are associated with more severe adverse reactions.

The use of nucleic acid technique, specifically mRNA has not yet been explored for *S. aureus* vaccine although this has been successful in the development of vaccines against other Gram-positive bacteria such as group A and B streptococci with significant immune response and transgenerational humoral immunity in mice (68). On the other hand, DNA vaccines have shown efficacy in pre-clinical trials in mice infections by stimulating $CD8^+$ T-cell responses (69), although this was not reproducible in humans (70).

Conclusion:

Our review showed that SSSS carries a mortality rate of <5% amongst children <5 years of age, as opposed to a mortality rate of >50% in affected adults. Penicillinase-resistant penicillins are recommended for the empirical treatment of SSSS. Administration of fresh frozen plasma (FFP) to neutralize staphylococcal exotoxins could aid early recovery. Several staphylococcal vaccine candidates are being developed and offer hope for providing specific protection against SSSS in future.

Contributions of authors:

AB conceived the review, designed the outline, wrote the aspects of abstract and conclusion, and reviewed the manuscript; MN searched the literature for relevant publications, wrote the aspects of introduction, epidemiology and clinical Features of SSSS; IJ searched the literature for relevant publications and wrote the materials and methods; TMB searched the literature for relevant publications, reviewed articles, and wrote the aspects of vaccine development against staphylococcal infections; BM searched the literature for relevant publications, reviewed articles, and the wrote the aspects of diagnosis, treatment and prognosis of SSSS.

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Authors declare no conflict of interest.

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