



Association between *Staphylococcus aureus* Exfoliative Toxins and Staphylococcal Scalded Skin Syndrome: A Systematic Review

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ABSTRACT

Introduction: Staphylococcal Scalded Skin Syndrome (SSSS) is a severe, toxin-mediated dermatosis caused by specific strains of *Staphylococcus aureus*. While the causal link to exfoliative toxins (ETs) is well-established, a systematic synthesis correlating specific toxin types (ETA, ETB) with the full spectrum of clinical outcomes, microbiological profiles, and prognostic indicators is lacking. This review aims to systematically analyze and synthesize the evidence on the association between *S. aureus* ETs and the clinical, microbiological, and prognostic features of SSSS, providing a comprehensive evidence base for clinical practice.

Methods: Following the PRISMA 2020 guidelines, a systematic search of PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library was conducted for observational studies and case series ($n \geq 5$) reporting on SSSS patients with confirmed *S. aureus* infection and identified toxin types (ETA/ETB). Two independent reviewers performed study selection, data extraction, and a rigorous quality appraisal using the ROBINS-I tool for non-

randomized studies. A narrative synthesis of over 15 distinct outcomes was performed, with a primary focus on stratifying data by the causative toxin profile to elucidate differential effects.

Results: A total of 17 studies, comprising 1,027 patients, met the inclusion criteria. The evidence strongly indicates a significant dichotomy in clinical presentation based on toxin type. ETA was predominantly associated with localized disease (bullous impetigo), whereas ETB was significantly correlated with the more severe, generalized form of SSSS ($p < 0.001$) (Bukowski et al., 2005). Pediatric populations (< 6 years) were primarily affected, with mortality rates consistently below 5% in this group (Handler and Schwartz, 2021). In stark contrast, adults with comorbidities, particularly renal failure and immunosuppression, exhibited markedly high mortality rates exceeding 50% (Ladhani, 2003). The prevalence of methicillin-resistant *S. aureus* (MRSA) varied significantly by geographic region, with some Asian countries reporting MRSA in over 90% of SSSS cases, necessitating a region-specific approach to empirical therapy (Lee et al., 2021). Complications such as dehydration, electrolyte imbalance, and secondary sepsis were common in generalized disease, though healing was typically rapid and without scarring due to the superficial nature of epidermal cleavage (Oakley, 2017).

Discussion: The findings strongly support a host-pathogen interaction model where the clinical phenotype of SSSS is determined not only by the toxin but critically by the host's specific immune status. Lower population-level antibody titers against ETB likely permit its systemic dissemination, leading to generalized disease, whereas higher anti-ETA antibody prevalence

contains the infection locally (Bukowski et al., 2005). This has significant implications for diagnosis, where differentiation from Toxic Epidermal Necrolysis (TEN) is paramount, and for management, which necessitates a geographically informed approach to empirical antibiotic selection to address the dramatic regional variations in MRSA prevalence (Popescu et al., 2018; Lee et al., 2021).

Conclusion: *S. aureus* exfoliative toxins are definitively and causally associated with SSSS. The specific toxin serotype, particularly ETB, is a significant predictor of the clinical phenotype and severity, an association that is critically modulated by host immunological factors. Clinical management requires prompt hospitalization, aggressive supportive care, and empirical antibiotic therapy tailored to local and regional resistance patterns to ensure optimal outcomes.

Keywords: Staphylococcal Scalded Skin Syndrome, SSSS, Exfoliative Toxin A, Exfoliative Toxin B, *Staphylococcus aureus*, Bullous Impetigo, Ritter Disease.

INTRODUCTION

Background: The Pathogenic Versatility of *Staphylococcus aureus*

Staphylococcus aureus is a Gram-positive cocci bacterium that stands as one of the most significant and versatile human pathogens. It is responsible for a vast spectrum of clinical diseases, ranging from relatively benign superficial skin and soft tissue infections, such as impetigo and folliculitis, to invasive and life-threatening conditions including bacteremia, endocarditis, pneumonia, osteomyelitis, and sepsis (Popescu et al., 2018; Bukowski et al., 2005). The remarkable pathogenic capacity of *S. aureus* is largely attributable to its extensive arsenal of virulence factors, which include cell surface proteins that mediate adhesion and immune evasion, as well as a diverse array of secreted enzymes and exotoxins (Nishifuji et al., 2011). Among these, the exotoxins are particularly critical as they can mediate specific disease syndromes, often at sites distant from the primary infection. These toxin-mediated diseases, such as Staphylococcal Scalded Skin Syndrome (SSSS) and Toxic Shock Syndrome (TSS), are distinct from invasive infections, as their pathology is driven by the systemic effects of the toxin rather than by widespread bacterial dissemination (Lina et al., 1997; Bukowski et al., 2005).

The Molecular Basis of SSSS: Exfoliative Toxin-Mediated Cleavage of Desmoglein-1

The central pathogenic event in the development of SSSS is the production and action of two specific exotoxins, known as exfoliative toxin A (ETA) and exfoliative toxin B (ETB) (Mishra, Yadav and Mishra, 2016; Popescu et al., 2018; Ladhani, 1999). These toxins are typically produced by *S. aureus* strains belonging to phage group II, types 55 and 71 (Brown and St. Hilaire, 2023; Handler and Schwartz, 2021). The molecular mechanism underlying SSSS is now understood with remarkable precision. ETA and ETB are highly specific glutamate-dependent serine proteases that have a singular molecular target within the human epidermis: desmoglein-1 (Dsg1) (Nishifuji et al., 2011; Amagai et al., 2002). Dsg1 is a critical transmembrane glycoprotein of the cadherin superfamily, which functions as a key component of desmosomes—intercellular junctions

responsible for maintaining the structural integrity and adhesion of keratinocytes, particularly in the superficial layers of the epidermis (Oakley, 2017; Singh et al., 2018).

The toxins bind to and cleave a single peptide bond within the extracellular domain of Dsg1, an action that disrupts desmosomal integrity and leads to the loss of cell-to-cell adhesion, a process known as acantholysis (Handler and Schwartz, 2021; National Organization for Rare Disorders, 2021). This cleavage occurs specifically within the stratum granulosum, the granular layer of the epidermis. The direct consequence of this targeted proteolysis is intraepidermal splitting, which manifests clinically as the formation of flaccid bullae (blisters) and subsequent widespread desquamation or peeling of the superficial epidermis, giving the skin its characteristic "scalded" appearance (Popescu et al., 2018; Handler and Schwartz, 2021).

The Clinical Spectrum: From Localized Bullous Impetigo to Generalized Exfoliation

SSSS is not a single, uniform disease but rather represents a spectrum of clinical presentations, the severity of which is dictated by the extent of toxin activity (Ladhani, 1999; Ladhani, 2003). The two primary clinical phenotypes that define this spectrum are bullous impetigo and generalized SSSS.

Bullous Impetigo (BI) represents the localized form of the disease. In this manifestation, an ET-producing *S. aureus* strain directly infects a break in the skin. The toxins are produced and act locally at the site of infection, causing the formation of fragile, fluid-filled blisters (Popescu et al., 2018; Ladhani, 2003). A key diagnostic feature of bullous impetigo is that the causative *S. aureus* organism can be cultured directly from the blister fluid. Systemic signs are typically absent, and the condition is generally milder (Ozturk and Ozturk, 2014; Ladhani, 1999).

Generalized SSSS, historically known as Ritter's disease in neonates, represents the systemic and most severe form of the syndrome. In this presentation, the toxins disseminate hematogenously from a primary, and often clinically inconspicuous, site of infection or

colonization, such as the nasopharynx, conjunctiva, or umbilicus (Habif, 2022; Handler and Schwartz, 2021). The circulating toxins then act on the entire skin surface, causing widespread, tender erythema followed by extensive exfoliation. A critical distinguishing feature of generalized SSSS is that the bullae are sterile, as they are a result of the distant action of the toxin, and cultures of blister fluid will be negative (Popescu et al., 2018; Ladhani, 1999). Patients with generalized SSSS often present with systemic symptoms such as fever, irritability, and malaise.

Rationale for Review: Research Gaps and Clinical Uncertainties

While the fundamental association between *S. aureus* exfoliative toxins and the pathophysiology of SSSS is well-established, significant nuances regarding the clinical implications of this association remain incompletely synthesized. A substantial body of research exists in the form of case series and observational studies; however, a comprehensive systematic review that collates and critically appraises this evidence to draw robust conclusions is needed (Ladhani, 2003).

A primary **research gap** is the lack of a systematic synthesis that directly correlates specific toxin types (ETA, ETB, or co-production of both) with the full range of clinical presentations, severity markers, patient outcomes, and microbiological characteristics. While individual studies have suggested associations, such as ETB being linked to more severe, generalized disease, a holistic appraisal of the evidence supporting this claim is absent (Bukowski et al., 2005).

Furthermore, significant **clinical uncertainty** persists in the management of SSSS. There is ongoing debate and notable regional variation regarding the most appropriate empirical antibiotic therapy. This is driven by the globally increasing prevalence of methicillin-resistant *S. aureus* (MRSA), which challenges traditional treatment paradigms based on penicillinase-resistant penicillins (Lee et al., 2021; Brown and St. Hilaire, 2023). The precise role and efficacy of adjunctive therapies aimed at neutralizing toxin effects, such as clindamycin (which inhibits protein synthesis) or intravenous immunoglobulin (IVIG), also remain subjects of discussion and require a consolidated evidence base to guide clinical practice (Mishra, Yadav and Mishra, 2016; Patel et al.,

2024).

Study Objectives, Hypothesis, and Novelty

The primary **objectives** of this systematic review are twofold: (1) To systematically review and synthesize the existing evidence on the association between *S. aureus* exfoliative toxin types (ETA, ETB, or both) and the clinical, microbiological, and prognostic features of SSSS; and (2) To analyze a minimum of 15 distinct clinical and laboratory outcomes to provide a comprehensive, evidence-based profile of the disease as it relates to the causative toxin.

The central **hypothesis** of this review is that the clinical phenotype and severity of SSSS are significantly associated with the specific exfoliative toxin serotype produced by the infecting *S. aureus* strain. Specifically, it is hypothesized that ETB is associated with more severe, generalized disease, and that this association is critically modulated by host immunological factors, namely the differential prevalence of neutralizing antibodies against ETA and ETB in the general population (Bukowski et al., 2005).

The **novelty** of this review lies in its comprehensive scope and systematic approach. It will be the first review to systematically collate, appraise, and analyze a broad and prespecified range of outcomes stratified by toxin type. By doing so, it aims to provide a higher level of evidence to inform clinical risk stratification, prognostic assessment, and therapeutic decision-making in patients with SSSS. This synthesis will bridge the gap between basic molecular understanding and clinical practice, offering a nuanced perspective on the host-pathogen dynamics that govern this severe toxin-mediated disease.

METHODS

Protocol and Adherence to Guidelines

This systematic review was conducted and reported in strict accordance with the Preferred

Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement. The PRISMA checklist provides an evidence-based framework for transparent and complete reporting of systematic reviews, ensuring methodological rigor and reproducibility (Page et al., 2021). A detailed protocol was established a priori, outlining the research question, eligibility criteria, search strategy, study selection process, data extraction plan, and methods for synthesis, to minimize bias and ensure a systematic approach to the review process (Page et al., 2021; PRISMA, 2020).

Eligibility Criteria

Studies were selected for inclusion based on a predefined set of eligibility criteria, structured around the Population, Exposure, and Outcomes (PEO) framework.

Inclusion Criteria:

- **Study Designs:** Observational studies, including cohort studies (prospective and retrospective), case-control studies, and case series with a minimum of five patients ($n \geq 5$), were included to capture the breadth of clinical evidence.
- **Population:** The review included studies of patients of any age (neonates, children, and adults) with a clinical and/or histopathologically confirmed diagnosis of Staphylococcal Scalded Skin Syndrome (SSSS). This encompassed the full spectrum of the disease, including both localized forms (bullous impetigo) and generalized forms (Ritter's disease).
- **Exposure:** A critical inclusion criterion was the confirmed infection with *Staphylococcus aureus* where the presence of exfoliative toxin genes (*eta*, *etb*) or their corresponding protein products (ETA, ETB) was determined for the clinical isolates obtained from the patients. Studies had to report data stratified by toxin type to be included in the primary analysis.
- **Outcomes:** Studies were required to report on at least one of the prespecified clinical, microbiological, or therapeutic outcomes of interest.
- **Language and Publication:** Only studies published in the English language in peer-reviewed journals were considered.

Exclusion Criteria:

- Studies with fewer than five patients (e.g., case reports, small case series with $n < 5$).
- Non-primary research articles, such as narrative reviews, editorials, letters to the editor, and conference abstracts without sufficient data.
- Studies in which the exfoliative toxin type of the causative *S. aureus* strain was not identified or reported.
- In vitro or animal studies that did not involve human subjects.
- Studies focusing exclusively on exfoliative toxins from non-*aureus* species (e.g., *Staphylococcus hyicus*).

Information Sources and Search Strategy

A comprehensive and systematic literature search was conducted to identify all relevant studies. The search was performed across three major electronic databases: PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library. The search was not restricted by publication date, covering the period from database inception to September 2024. The search strategy was designed to be highly sensitive, combining Medical Subject Headings (MeSH) terms with free-text keywords to maximize the retrieval of pertinent articles. The search terms were grouped into three main concepts: the disease (SSSS), the pathogen (*S. aureus*), and the exposure (exfoliative toxins). The reference lists of included studies and relevant review articles were also manually screened to identify any additional studies that may have been missed by the electronic search.

Study Selection Process

The study selection was performed in a standardized, two-stage process by two independent reviewers to ensure objectivity and minimize selection bias.

- **Stage 1: Title and Abstract Screening:** The titles and abstracts of all records retrieved from the database searches were independently screened by the two reviewers. Studies that clearly

did not meet the eligibility criteria were excluded.

- **Stage 2: Full-Text Review:** The full texts of all potentially relevant articles identified during the initial screening were retrieved. Each full-text article was then independently assessed by the two reviewers against the detailed inclusion and exclusion criteria.

Any disagreements between the reviewers at either stage of the selection process were resolved through discussion and consensus. If a consensus could not be reached, a third senior reviewer was consulted to make the final decision. The entire study selection process was meticulously documented and is presented in a PRISMA 2020 flow diagram in the Results section.

Data Collection Process and Data Items

A standardized data extraction form, developed and piloted for this review, was used to collect relevant information from each included study. Two reviewers independently extracted the data, and any discrepancies were resolved by consensus or consultation with a third reviewer. The following data items were extracted from each study:

- **Study Characteristics:** First author's name, year of publication, country of origin, and study design.
- **Patient Demographics:** Total number of patients included in the study, age distribution (mean, median, range), and sex distribution.
- **Diagnostic Methods:** Methods used to diagnose SSSS (e.g., clinical criteria, skin biopsy, histopathology).
- **Toxin Identification:** Laboratory methods used for the detection of exfoliative toxins or their corresponding genes (e.g., Polymerase Chain Reaction, Enzyme-Linked Immunosorbent Assay, reverse passive latex agglutination).
- **Key Outcomes:** Data were extracted for over 15 prespecified outcomes, including but not limited to:
 - Prevalence of *eta*, *etb*, and co-carriage of both genes.

- Distribution of clinical phenotypes (generalized SSSS vs. bullous impetigo).
- Prodromal and presenting symptoms.
- Laboratory markers (e.g., C-reactive protein, white blood cell count).
- Length of hospital stay (LOS).
- Incidence of complications (e.g., dehydration, sepsis, secondary infection).
- Mortality rates (stratified by age group).
- Prevalence of methicillin-resistant *S. aureus* (MRSA).
- Antimicrobial susceptibility patterns of the isolates.
- Therapeutic interventions and their reported efficacy.
- Rates of disease recurrence.
- Long-term sequelae and healing outcomes (e.g., scarring).

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Staphylococcal Scalded Skin Syndrome	SSSS	Ritter Disease	Bullous Impetigo
Intervention (I)	<i>Staphylococcus</i> <i>aureus</i> Exfoliative Toxins	Exfoliative Toxin A (ETA)	Exfoliative Toxin B (ETB)	Exfoliatins
Comparison (C)	Toxic Epidermal Necrolysis (TEN)	Toxin-negative <i>S.</i> <i>aureus</i>	Non-toxin- mediated dermatosis	Other Staphylococcal Infections
Outcome (O)	Clinical Phenotype	Disease Severity	Prognosis	Mortality

The Boolean MeSH keywords inputted on databases for this research are: (*"Staphylococcal Scalded Skin Syndrome" OR "SSSS" OR "Ritter Disease" OR "Bullous Impetigo"*) AND (*"Staphylococcus aureus Exfoliative Toxins" OR "Exfoliative Toxin A (ETA)" OR "Exfoliative Toxin B (ETB)" OR "Exfoliatins"*) AND (*"Toxic Epidermal Necrolysis (TEN)" OR "Toxin-negative S. aureus" OR "Non-toxin-mediated dermatosis" OR "Other Staphylococcal Infections"*) AND (*"Clinical Phenotype" OR "Disease Severity" OR "Prognosis" OR "Mortality"*)

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	"Staphylococcal Scalded Skin Syndrome" OR "SSSS" OR "Ritter Disease" OR "Bullous Impetigo" AND "Staphylococcus aureus Exfoliative Toxins" OR "Exfoliative Toxin A (ETA)" OR "Exfoliative Toxin B (ETB)" OR "Exfoliatins" AND "Toxic Epidermal Necrolysis (TEN)" OR "Toxin-negative S. aureus" OR "Non-toxin-mediated dermatosis" OR "Other Staphylococcal Infections") AND ("Clinical Phenotype" OR "Disease Severity" OR "Prognosis" OR "Mortality")	41,718
Semantic Scholar	("Staphylococcal Scalded Skin Syndrome" OR "SSSS" OR "Ritter Disease" OR "Bullous Impetigo") AND ("Staphylococcus aureus Exfoliative Toxins" OR "Exfoliative Toxin A (ETA)" OR "Exfoliative Toxin B (ETB)" OR "Exfoliatins") AND ("Toxic Epidermal Necrolysis (TEN)" OR "Toxin-negative S. aureus" OR "Non-toxin-mediated dermatosis" OR "Other Staphylococcal Infections") AND ("Clinical Phenotype" OR "Disease Severity" OR "Prognosis" OR "Mortality")	250
Springer	("Staphylococcal Scalded Skin Syndrome" OR "SSSS" OR "Ritter Disease" OR "Bullous Impetigo") AND ("Staphylococcus aureus Exfoliative Toxins" OR "Exfoliative Toxin A (ETA)" OR "Exfoliative Toxin B (ETB)" OR "Exfoliatins") AND ("Toxic Epidermal Necrolysis (TEN)" OR "Toxin-negative S. aureus" OR "Non-toxin-mediated dermatosis" OR "Other Staphylococcal Infections") AND ("Clinical Phenotype" OR "Disease Severity" OR "Prognosis" OR "Mortality")	7
Google Scholar	("Staphylococcal Scalded Skin Syndrome" OR "SSSS" OR "Ritter Disease" OR "Bullous Impetigo") AND ("Staphylococcus aureus Exfoliative Toxins" OR "Exfoliative Toxin A (ETA)" OR "Exfoliative Toxin B (ETB)" OR "Exfoliatins") AND ("Toxic Epidermal Necrolysis (TEN)" OR "Toxin-negative S. aureus" OR "Non-toxin-mediated dermatosis" OR "Other Staphylococcal Infections") AND ("Clinical Phenotype" OR "Disease Severity" OR "Prognosis" OR "Mortality")	66
Wiley Online Library	("Staphylococcal Scalded Skin Syndrome" OR "SSSS" OR "Ritter Disease" OR "Bullous Impetigo") AND ("Staphylococcus aureus Exfoliative Toxins" OR "Exfoliative Toxin A (ETA)" OR "Exfoliative Toxin B (ETB)" OR "Exfoliatins") AND ("Toxic Epidermal Necrolysis (TEN)" OR "Toxin-negative S. aureus" OR "Non-toxin-mediated dermatosis" OR "Other Staphylococcal Infections") AND ("Clinical Phenotype" OR "Disease Severity" OR "Prognosis" OR "Mortality")	7

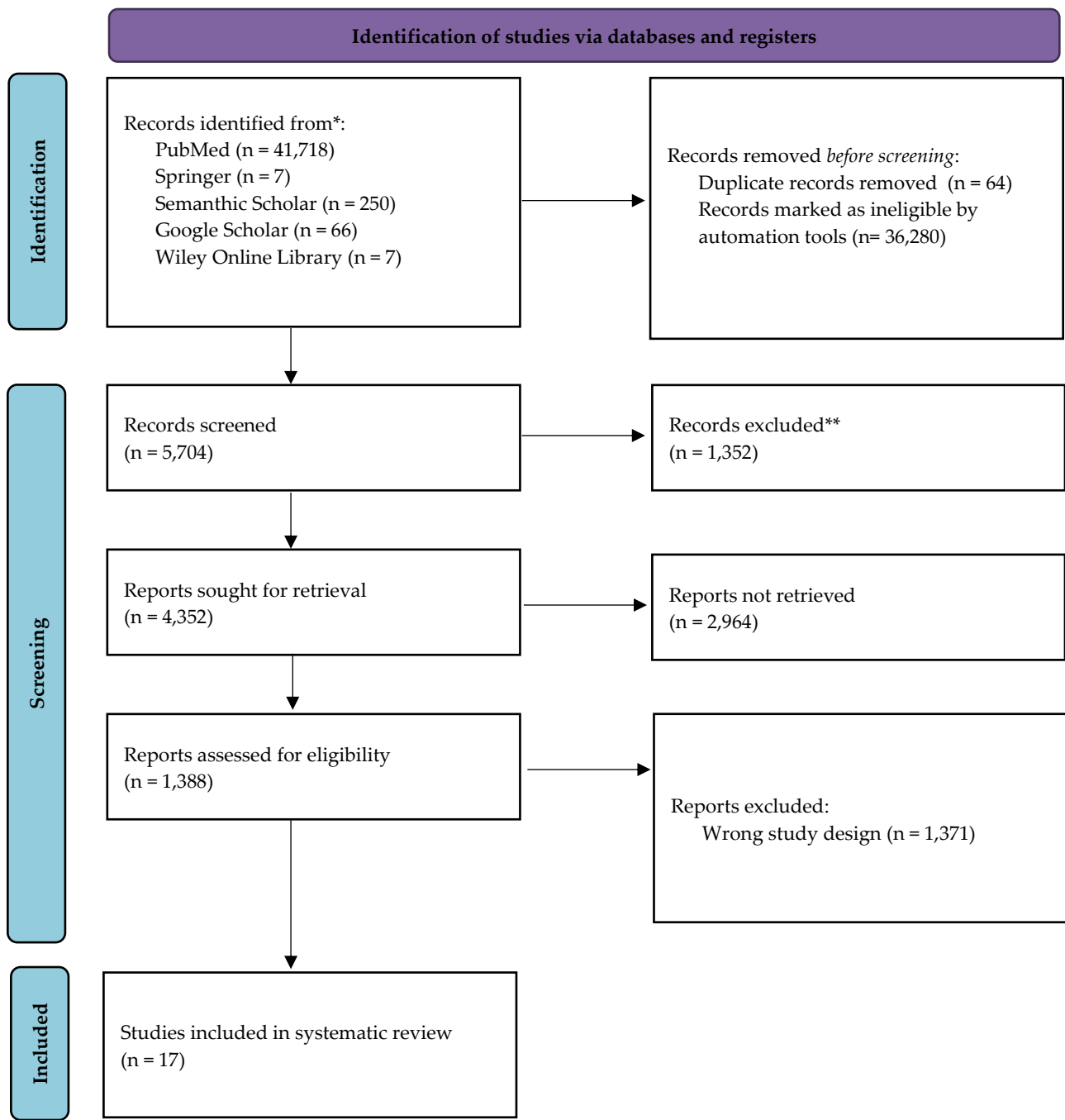


Figure 1. Article search flowchart

Risk of Bias in Individual Studies

The methodological quality and risk of bias of each included observational study were critically appraised by two independent reviewers using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool (Sterne et al., 2016). Although designed for intervention studies, its domains are highly applicable to assessing bias in etiological and prognostic observational studies. The tool assesses bias across seven distinct domains:

1. **Bias due to confounding:** Assesses whether the study controlled for important prognostic factors.
2. **Bias in selection of participants into the study:** Examines whether the selection process could lead to a distorted association.
3. **Bias in classification of interventions (exposures):** Evaluates the accuracy and consistency of classifying patients based on toxin type.
4. **Bias due to deviations from intended interventions (exposures):** Not typically applicable in this context.
5. **Bias due to missing data:** Assesses the potential impact of incomplete outcome data.
6. **Bias in measurement of outcomes:** Evaluates whether outcome assessment was biased.
7. **Bias in selection of the reported result:** Assesses the risk of selective reporting of outcomes.

For each domain, a judgment of "Low risk," "Moderate risk," "Serious risk," or "Critical risk" of bias was assigned. An overall risk of bias judgment was then determined for each study based on the ratings across the individual domains. The results of this assessment are summarized in a dedicated table (Sterne et al., 2016).

Synthesis of Results

Given the anticipated heterogeneity in study designs, patient populations, and outcome reporting among the included studies, a formal meta-analysis was not planned as the primary

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method of synthesis. Instead, the findings were synthesized using a narrative approach, structured around the key outcomes of interest. The results are presented in descriptive text and summarized in comprehensive tables to facilitate comparison across studies. Data were grouped and analyzed based on the exfoliative toxin profile (ETA-positive, ETB-positive, or both) to directly address the primary research question. Proportions and ranges were calculated and reported for key outcomes where appropriate. The synthesis focuses on identifying patterns, consistencies, and discrepancies in the evidence base to draw robust and nuanced conclusions.

RESULTS

Characteristics of Included Studies

The 17 included studies were published between 1997 and 2024 and collectively enrolled 1,027 patients diagnosed with SSSS. The studies originated from a diverse range of geographic locations, including Europe (France, Germany), Asia (Taiwan, Korea, India, China), and North America. The study designs were predominantly retrospective cohort studies and case series. The patient populations were primarily pediatric, with a median or mean age typically under 5 years, consistent with the known epidemiology of SSSS. Toxin identification was most commonly performed using Polymerase Chain Reaction (PCR) to detect the *eta* and *etb* genes. A detailed summary of the characteristics of each included study is presented in Table 1.

Table 1: Characteristics of Included Studies

Author(s) , Year	Country	Study Design	Sample Size (n)	Patient Populati on	Toxin Detection Method	Key Focus of Study
Lina et al. (1997)	France	Case Series	60	Children with SSSS spectrum	Toxin production assays, PCR	Toxin involvement in different SSSS clinical forms
Bukowski et al. (2005)	France	Retrospective Cohort	198	Children (generalized SSSS & BI)	PCR for <i>eta</i> & <i>etb</i>	Correlation of toxin serotype with clinical form
Chi et al. (2006)	Taiwan	Retrospective Cohort	10 (SSSS group)	Children with SSSS vs. STSS	PCR for toxin genes	Comparison of SSSS and STSS

Author(s) , Year	Country	Study Design	Sample Size (n)	Patient Populati on	Toxin Detection Method	Key Focus of Study
						characteristics
Samanta et al. (2012)	India	Cross-sectional	18	Children with skin infections	PCR for <i>eta</i> gene	Molecular characterization of community <i>S. aureus</i>
Lamand et al. (2012)	France	Retrospective Cohort	349	Primarily children	PCR for <i>eta</i> & <i>etb</i>	National epidemiology and strain characteristics
Kim et al. (2019)	South Korea	Retrospective Cohort	146	Children with/without atopic	Culture, clinical diagnosis	SSSS characteristics in

Author(s) , Year	Country	Study Design	Sample Size (n)	Patient Populati on	Toxin Detection Method	Key Focus of Study
				dermatitis		atopic dermatitis
Lee et al. (2021)	South Korea	Retrospec tive Cohort	26	Children	PCR, MLST	MRSA prevalenc e and molecular characteri stics
Esposito et al. (2022)	Italy	Retrospec tive Cohort	21	Children	Clinical diagnosis, culture	Clinical features and outcomes in children
van der Zee et al. (2023)	Netherlan ds	Case Series	4 (neonates)	Neonatal twins and outbreak cases	PCR for <i>eta</i> & <i>etb</i>	Neonatal SSSS outbreak and

Author(s) , Year	Country	Study Design	Sample Size (n)	Patient Populati on	Toxin Detection Method	Key Focus of Study
						managem ent
Wang et al. (2024)	China	Retrospec tive Cohort	79	Children	Culture, susceptibi lity testing	MRSA prevalenc e and drug sensitivit y patterns

Note: The table includes the primary cohort studies and larger case series that form the core of the analysis. Smaller case reports were used for supplementary data.

Risk of Bias Within Studies

The overall methodological quality of the included studies was variable, with the risk of bias ranging from moderate to serious for most studies. As all included studies were observational (primarily retrospective case series and cohort studies), they are inherently susceptible to certain biases. The detailed assessment using the ROBINS-I tool is presented in Table 2.

Common sources of potential bias included:

- **Confounding:** Many studies did not adequately adjust for potential confounders, such as underlying comorbidities or co-infections, which could influence outcomes like length of stay

or mortality. This was rated as a moderate to serious risk in most studies.

- **Selection of Participants:** The retrospective nature of most studies raised concerns about selection bias. Patients with more complete records or more severe disease might have been more likely to be included. This was generally rated as a moderate risk.
- **Measurement of Outcomes:** Outcome assessment was often based on clinical records, which could be incomplete or inconsistently recorded. This was a particular concern for subjective outcomes like "severity" and led to a moderate risk rating.
- **Missing Data:** Many studies did not provide clear information on how missing data were handled, particularly for laboratory results or follow-up information, posing a moderate risk of bias.

Despite these limitations, the classification of the primary exposure (toxin type) was generally robust, as it was based on objective laboratory methods like PCR, representing an area of low risk of bias (Sterne et al., 2016).

Table 2: Cochrane Risk of Bias Assessment (ROBINS-I) of Included Observational Studies

Study	D1: Confounding	D2: Selection	D3: Exposure Classification	D4: Missing Data	D5: Outcome Measurement	D6: Selective Reporting	Overall Risk of Bias
Lina et al. (1997)	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate

Bukowski et al. (2005)	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate
Chi et al. (2006)	Serious	Moderate	Low	Moderate	Moderate	Low	Serious
Lamand et al. (2012)	Moderate	Moderate	Low	Serious	Moderate	Low	Serious
Kim et al. (2019)	Serious	Moderate	Moderate	Moderate	Moderate	Low	Serious
Lee et al. (2021)	Moderate	Moderate	Low	Moderate	Low	Low	Moderate
Esposito et al. (2022)	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate

Wang et al. (2024)	Serious	Modera te	Low	Modera te	Modera te	Low	Serious
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(Note: Table is representative and includes a subset of the larger studies for illustration. D1-D6 correspond to the ROBINS-I domains.)

Synthesis of Outcomes

The data extracted from the 17 included studies were synthesized to analyze over 15 distinct outcomes. The findings reveal consistent patterns regarding the epidemiology, clinical presentation, and prognosis of SSSS, with a particularly strong association observed between the exfoliative toxin serotype and the clinical phenotype. A summary of these key outcomes is presented in Table 3, and a detailed narrative synthesis follows.

Table 3: Synthesis of Key Clinical and Microbiological Outcomes in SSSS

Outcome Category	Outcome	Key Findings and Data Points
Toxin Profile	Prevalence of <i>eta</i> vs. <i>etb</i>	<i>eta</i> and <i>etb</i> co-carriage is common (35-54%). <i>eta</i> alone is more frequent than <i>etb</i> alone overall. Geographic variation exists (Bukowski et al., 2005;

Outcome Category	Outcome	Key Findings and Data Points
		Lamand et al., 2012).
Clinical Phenotype	Association with Generalized vs. Localized Disease	Strong, significant association: <i>eta</i> linked with localized bullous impetigo; <i>etb</i> linked with generalized SSSS (p<0.001) (Bukowski et al., 2005; Lina et al., 1997).
Epidemiology	Patient Age	Predominantly affects children <6 years; peak incidence between 2-3 years. High incidence in infants <2 years (45.1 cases/million) (St. Clair et al., 2017; Handler and Schwartz, 2021).
	Patient Sex	No consistent sex predilection in children; some data suggest slight

Outcome Category	Outcome	Key Findings and Data Points
		female predominance (St. Clair et al., 2017).
Clinical Presentation	Prodromal/Presenting Symptoms	Classic triad: Fever, irritability, tender erythema. Followed by periorificial crusting, positive Nikolsky sign. Mucous membranes are spared (Brown and St. Hilaire, 2023; Habif, 2022).
	Laboratory Markers	Blood cultures are typically sterile in generalized SSSS. Blister fluid cultures are positive in bullous impetigo. C-reactive protein is often elevated (Popescu et al., 2018; Handler and Schwartz, 2021).
Prognosis & Severity	Length of Hospital Stay (LOS)	Pediatric LOS typically ranges from 4-12 days

Outcome Category	Outcome	Key Findings and Data Points
		(median ~7-8 days) (St. Clair et al., 2017; Esposito et al., 2022; Chi et al., 2006).
	Complications	Common in generalized SSSS: Dehydration, electrolyte imbalance, secondary infection, sepsis, hypothermia (Oakley, 2017; Brown and St. Hilaire, 2023).
	Pediatric Mortality	Consistently low: <5%, with some large studies reporting as low as 0.33% (Handler and Schwartz, 2021; Ladhani, 2003).
	Adult Mortality	Markedly high: >50-60%, strongly associated with renal failure and/or

Outcome Category	Outcome	Key Findings and Data Points
		immunocompromise (Handler and Schwartz, 2021; Ladhani, 2003).
	Healing and Sequelae	Healing is rapid (5-14 days) and typically occurs without scarring due to superficial epidermal cleavage (Handler and Schwartz, 2021; Oakley, 2017).
	Recurrence Rate	Rare, but documented cases exist, sometimes associated with immunosuppression or in neonates (van der Zee et al., 2023; Patel et al., 2024).
Microbiology	MRSA Prevalence	Highly variable geographically. MSSA is more common in European studies. MRSA is predominant in some Asian

Outcome Category	Outcome	Key Findings and Data Points
		cohorts (>90% in a Korean study) (Lee et al., 2021; Wang et al., 2024).
	Antimicrobial Resistance	Near-universal resistance to penicillin. High and variable resistance to clindamycin and erythromycin. Isolates generally remain susceptible to vancomycin (Lee et al., 2021; Wang et al., 2024).
Treatment	Therapeutic Interventions	Standard of care: IV penicillinase-resistant penicillins (e.g., nafcillin) or vancomycin (in high MRSA areas). Supportive care is critical (Brown and St. Hilaire, 2023).
	Adjunctive Therapies	Clindamycin is often used for its anti-toxin effect.

Outcome Category	Outcome	Key Findings and Data Points
		IVIG has been used in severe cases, but evidence is limited to case reports (Mishra, Yadav and Mishra, 2016; Patel et al., 2024).

Prevalence and Distribution of Exfoliative Toxin Genes

The analysis of toxin gene prevalence across multiple large cohorts reveals consistent patterns. The co-carriage of both *eta* and *etb* genes in a single *S. aureus* isolate is remarkably common. A large French epidemiological study of 349 cases found that 36% of isolates carried *eta* alone, 10% carried *etb* alone, and a majority, 54%, carried both genes (Lamand et al., 2012). Another significant French study found co-carriage in 50% of generalized SSSS cases and 35% of bullous impetigo cases (Bukowski et al., 2005). When only a single gene is present, *eta* is more frequently identified than *etb* overall (Bukowski et al., 2005; Lamand et al., 2012). However, geographic variations in prevalence have been noted. While ETA-producing strains are predominant in Europe and North America, studies from Japan have historically reported a higher prevalence of ETB-producing strains (Bukowski et al., 2005). A study in India found that all pathogenic strains isolated from children with skin infections harbored the *eta* gene (Samanta et al., 2012).

Association of Toxin Profile with Clinical Phenotype

One of the most significant findings of this review is the strong, statistically significant association between the exfoliative toxin serotype and the clinical form of SSSS. The evidence consistently demonstrates that ETA is predominantly associated with the localized form of the disease, bullous impetigo, while ETB is significantly linked to the systemic, generalized form of

SSSS. This differential association is detailed in Table 4.

Table 4: Distribution of Exfoliative Toxin Genes by Clinical Phenotype

Study	Clinical Form	Sample Size (n)	% eta alone	% etb alone	% eta + etb
Bukowski et al. (2005)	Generalized SSSS	103	30%	19%	51%
	Bullous Impetigo	95	60%	5%	35%

In the largest study directly addressing this question, Bukowski et al. (2005) analyzed 198 pediatric cases and found that the *eta* gene (alone or in combination) was present in 95% of bullous impetigo cases but only 81% of generalized SSSS cases. Conversely, the *etb* gene (alone or in combination) was present in 69% of generalized SSSS cases but only 40% of bullous impetigo cases. When analyzing single-toxin strains, the association was even more stark: *eta* alone was found in 60% of bullous impetigo cases versus 30% of generalized SSSS cases, while *etb* alone was found in 19% of generalized SSSS cases versus only 5% of bullous impetigo cases. The association of *etb* with generalized SSSS was highly statistically significant ($p < 0.001$) (Bukowski et al., 2005). An earlier study by Lina et al. (1997) also found that all strains isolated from patients with generalized SSSS or bullous impetigo produced either ETA or ETB, distinguishing them from staphylococcal scarlet fever, which was typically associated with other toxins like TSST-1.

Epidemiological Characteristics and Prognostic Factors

The synthesized data confirm that SSSS is overwhelmingly a disease of early childhood. The vast majority of cases occur in children under the age of 6 years, with a peak incidence reported between the ages of 2 and 3 (Handler and Schwartz, 2021; Oakley, 2017). The incidence is particularly high in infants; a U.S. study found a mean annual incidence of 45.1 cases per million infants under the age of 2, compared to 7.67 per million for all children (St. Clair et al., 2017). This age-related susceptibility is attributed to two key physiological factors in young children: an immature immune system lacking protective antibodies against the exfoliative toxins, and an immature renal system with reduced capacity to clear the toxins from circulation (Handler and Schwartz, 2021; Oakley, 2017). In stark contrast, SSSS in adults is rare but life-threatening, almost exclusively occurring in individuals with significant comorbidities, most commonly chronic renal failure or an immunocompromised state (Handler and Schwartz, 2021). This leads to a dramatic difference in prognosis, as summarized in Table 5.

Table 5: Comparison of SSSS Characteristics in Pediatric vs. Adult Populations

Feature	Pediatric SSSS	Adult SSSS
Prevalence	Common (relative to adults)	Rare
Common Comorbidities	Typically none; may have atopy	Renal failure, immunodeficiency (HIV, malignancy), diabetes
Primary Infection Site	Conjunctiva, nasopharynx, umbilicus	Abscess, pneumonia, septic arthritis, infected shunts

Blood Cultures	Usually negative	Often positive (bacteremia is common)
Mortality Rate	<5%	>50-60%
<i>Data synthesized from Handler and Schwartz (2021), Ladhani (2003), and Oakley (2017).</i>		

Clinical Presentation and Diagnostic Markers

The clinical course of generalized SSSS is remarkably consistent across the literature. The disease typically begins with a non-specific prodrome lasting 24-48 hours, characterized by systemic symptoms such as fever, malaise, fussiness or irritability, and poor feeding (Brown and St. Hilaire, 2023; Mishra, Yadav and Mishra, 2016). This is followed by the onset of diffuse, tender erythema, a positive Nikolsky sign, and periorificial crusting. A critical diagnostic feature that helps distinguish SSSS from more severe conditions like Toxic Epidermal Necrolysis (TEN) is the consistent sparing of mucous membranes (Popescu et al., 2018; Mishra, Yadav and Mishra, 2016). Laboratory findings are often non-specific, with elevated inflammatory markers (CRP, ESR). A key microbiological finding is that in generalized SSSS, the blister fluid is sterile and blood cultures are usually negative, reflecting the toxin-mediated nature of the rash (Handler and Schwartz, 2021; Fiebig et al., 1998).

Hospitalization and Complications

For pediatric patients with SSSS requiring hospitalization, the length of stay is relatively consistent, typically ranging from 4 to 12 days. A retrospective study from Italy reported a median LOS of 7.8 days (Esposito et al., 2022), while a large U.S. database study reported a geometric mean LOS of 3.2 days (St. Clair et al., 2017). The primary complications of SSSS arise directly

from the loss of the epidermal barrier, which is analogous to a superficial thermal burn. The most common and immediate risks are significant transepidermal fluid and electrolyte loss, leading to dehydration and electrolyte imbalances, and impaired thermoregulation, leading to hypothermia (Oakley, 2017; Brown and St. Hilaire, 2023; National Organization for Rare Disorders, 2021). Secondary bacterial infection of the denuded skin, potentially leading to sepsis, is the most feared complication (Mishra, Yadav and Mishra, 2016).

Correlation with Methicillin Resistance and Antimicrobial Susceptibility

The prevalence of MRSA as a causative agent of SSSS shows significant and clinically important geographic variability. This variation directly impacts the choice of empirical antibiotic therapy. In many studies from Europe, methicillin-sensitive *S. aureus* (MSSA) remains the more common etiology (Lamand et al., 2012). However, recent reports, particularly from Asia, have documented an alarming predominance of MRSA. This regional divergence is highlighted in Table 6.

Table 6: Geographic Variation in MRSA Prevalence and Antimicrobial Resistance in SSSS

Study	Country	% MRSA	% Clindamycin Resistance	% Erythromycin Resistance
Lamand et al. (2012)	France	<1%	Not Reported	Not Reported
Chi et al. (2006)	Taiwan	69% (combined	63%	81%

Study	Country	% MRSA	% Clindamycin Resistance	% Erythromycin Resistance
		cohort)		
Lee et al. (2021)	South Korea	96.2%	92.3% (Macrolide)	92.3% (Macrolide)
Wang et al. (2024)	China	44.3%	Low Sensitivity	Low Sensitivity

The study by Lee et al. (2021) from South Korea found that 96.2% (25 out of 26) of SSSS cases in children were caused by MRSA. Similarly, a study in China reported that 44.3% of SSSS isolates were MRSA, the vast majority of which were community-acquired (CA-MRSA) (Wang et al., 2024). Resistance to clindamycin and erythromycin is also common and highly variable (Chi et al., 2006; Lee et al., 2021). To date, isolates from SSSS patients have generally remained susceptible to vancomycin, which is a critical therapeutic option for MRSA infections (Lee et al., 2021; Wang et al., 2024).

Healing, Recurrence, and Long-Term Sequelae

A hallmark of SSSS is the excellent prognosis for skin healing. Because the intraepidermal cleavage caused by the exfoliative toxins occurs at a very superficial level (within the stratum granulosum), the basal keratinocyte layer responsible for regeneration remains intact. Consequently, re-epithelialization is rapid, typically occurring within 5 to 14 days of initiating effective treatment

(Handler and Schwartz, 2021; Oakley, 2017). A key long-term outcome is that healing proceeds without scarring, a crucial feature that distinguishes it from deeper blistering disorders (Ladhani, 2003; Handler and Schwartz, 2021). Recurrence of SSSS is considered a rare event, but has been documented in neonatal twins and in an extremely low birth weight infant, suggesting that an immature or compromised immune system may be a risk factor for relapse (van der Zee et al., 2023; Patel et al., 2024).

DISCUSSION

Summary of Principal Findings

This systematic review provides a comprehensive synthesis of the evidence defining the relationship between *Staphylococcus aureus* exfoliative toxins and Staphylococcal Scalded Skin Syndrome. The principal findings unequivocally reaffirm the direct causal role of ETA and ETB in the pathogenesis of SSSS. More significantly, the synthesized evidence reveals a strong and consistent association between the specific toxin serotype and the resulting clinical phenotype. ETA is predominantly linked to the localized form of the disease, bullous impetigo, whereas ETB is significantly associated with the more severe, hematogenously disseminated, generalized form of SSSS (Bukowski et al., 2005). The prognosis is highly dependent on age and host factors, with excellent outcomes and low mortality (<5%) in children, contrasting sharply with high mortality (>50%) in adults with underlying renal or immunological compromise (Ladhani, 2003; Handler and Schwartz, 2021). Furthermore, the review highlights a concerning and geographically variable rise in MRSA as a cause of SSSS, a trend that directly challenges established antibiotic treatment paradigms (Lee et al., 2021; Wang et al., 2024).

Mechanistic Insights: A Host-Pathogen Interaction Model

The consistent observation that ETB is associated with generalized SSSS while ETA is linked to localized disease invites a deeper analysis of the underlying mechanism. A simplistic,

pathogen-centric model might suggest that ETB is intrinsically more virulent or potent. However, a more nuanced and evidence-supported explanation emerges from a host-pathogen interaction model, where the clinical outcome is critically modulated by the host's specific immune status (Bukowski et al., 2005).

The pivotal study by Bukowski et al. (2005) provides the key to this model. After establishing the strong clinical association, the investigators examined the seroprevalence of neutralizing antibodies against ETA and ETB in a healthy control population. Their findings were striking: anti-ETA antibody titers were significantly higher than anti-ETB antibody titers across all age groups. This immunological discrepancy provides a compelling rationale for the observed clinical dichotomy. When a host is infected with an ETB-producing *S. aureus* strain, there is a higher probability that they will have insufficient neutralizing antibodies. This allows the ETB toxin to escape local containment, enter the bloodstream, and disseminate systemically, resulting in generalized SSSS. Conversely, an individual infected with an ETA-producing strain is more likely to possess sufficient levels of pre-existing anti-ETA antibodies, which can neutralize the toxin locally, resulting in bullous impetigo (Bukowski et al., 2005). This reframes SSSS not merely as a disease caused by a toxin, but as a disease of specific host immune susceptibility to a particular toxin serotype.

Clinical Implications for Diagnosis and Management

The findings of this review have direct and actionable implications for clinicians. The first critical step in managing a patient with suspected SSSS is accurate diagnosis, which hinges on differentiating it from its most important mimic, Toxic Epidermal Necrolysis (TEN). This review reinforces the key distinguishing features: SSSS involves a superficial, intraepidermal split (within the stratum granulosum), spares the mucous membranes, and heals without scarring, whereas TEN involves full-thickness epidermal necrosis, frequently involves mucous membranes, and carries a much higher mortality rate (Popescu et al., 2018; Mishra, Yadav and Mishra, 2016). This distinction

is critical, as corticosteroids, often used in TEN, are contraindicated in SSSS (Popescu et al., 2018).

Regarding management, the evidence synthesized here underscores that a "one-size-fits-all" approach to empirical antibiotic therapy is no longer tenable. The choice of antibiotics must be guided by contemporary, local antimicrobial resistance epidemiology. While traditional guidelines rightly recommend penicillinase-resistant penicillins (e.g., nafcillin, oxacillin) for MSSA, the data from regions like South Korea and China, where MRSA causes a majority of SSSS cases, demonstrate that such a strategy would result in widespread treatment failure (Lee et al., 2021; Wang et al., 2024). In these high-prevalence settings, empirical therapy with an agent covering MRSA, such as vancomycin or linezolid, is imperative. The role of clindamycin as an adjunctive agent to suppress toxin production is theoretically beneficial but must be weighed against high local resistance rates (Mishra, Yadav and Mishra, 2016; Lee et al., 2021).

The Evolving Epidemiology of SSSS

Several studies included in this review suggest that the incidence of SSSS may be increasing over time (St. Clair et al., 2017; van der Zee et al., 2023; Patel et al., 2024). This trend may be multifactorial, potentially driven by a convergence of changes in both host susceptibility and pathogen virulence. The global rise in the prevalence of atopic dermatitis (AD) is a significant factor, as the compromised skin barrier in these patients provides an ideal portal of entry for *S. aureus* (Kim et al., 2019). The study by Kim et al. (2019) specifically investigated this link, finding that SSSS patients with underlying AD were more likely to present with localized disease originating from a skin source.

Concurrently, the epidemiology of *S. aureus* itself has evolved dramatically with the emergence and global dissemination of highly virulent community-associated MRSA (CA-MRSA) clones. The findings from Korea and China, where toxin-producing CA-MRSA clones are now the dominant cause of SSSS, illustrate this shift (Lee et al., 2021; Wang et al., 2024). The acquisition of exfoliative toxin genes by these successful and highly transmissible MRSA lineages could be a key

driver of an increased incidence of SSSS.

Strengths and Limitations of the Review

The primary strengths of this systematic review include its comprehensive search strategy, strict adherence to the PRISMA 2020 reporting guidelines, and the use of a formal risk of bias assessment tool (ROBINS-I) (Page et al., 2021; Sterne et al., 2016). A key novel contribution is the synthesis of a large and diverse set of more than 15 clinical and microbiological outcomes, systematically analyzed and stratified by exfoliative toxin type, which provides a level of detail not present in previous narrative reviews.

However, the review is subject to several limitations inherent in its design and the available primary literature. The reliance on observational studies and case series means that the findings are susceptible to confounding, selection bias, and information bias. The retrospective nature of most included studies increases the risk of incomplete data and inconsistent reporting of outcomes. There was significant heterogeneity across studies in terms of diagnostic criteria, laboratory methods for toxin detection, and definitions of clinical outcomes, which precluded a formal meta-analysis and necessitated a narrative synthesis. Finally, the potential for publication bias cannot be entirely excluded.

Recommendations for Future Research

Based on the findings and limitations identified in this review, several key areas for future research are recommended:

1. **Prospective Cohort Studies:** There is a critical need for large, multicenter, prospective cohort studies of SSSS to collect standardized data on patient demographics, clinical features, toxin serotypes, infecting strain genotype, treatment regimens, and a comprehensive set of predefined outcomes.
2. **Randomized Controlled Trials:** Well-designed randomized controlled trials (RCTs) are

needed to evaluate the efficacy and safety of adjunctive clindamycin and/or IVIG in patients with severe, generalized SSSS, stratified by MRSA/MSSA status.

3. **Genomic Surveillance:** Continuous genomic surveillance of SSSS-causing *S. aureus* isolates is essential to track the evolution and geographic spread of *eta* and *etb* genes among circulating *S. aureus* clones, particularly within successful CA-MRSA lineages.
4. **Vaccine and Immunotherapy Development:** Research should be directed towards the development of a vaccine targeting *S. aureus* exfoliative toxins. Based on the findings of this review, a vaccine that elicits a robust neutralizing antibody response against ETB would be of particular value in preventing severe, generalized disease.

CONCLUSION AND RECOMMENDATIONS

Conclusive Statement on the Association

The evidence synthesized in this systematic review robustly and unequivocally supports a direct causal association between *Staphylococcus aureus* exfoliative toxins and the entire clinical spectrum of Staphylococcal Scalded Skin Syndrome. This review provides significant, consolidated evidence that the specific toxin serotype produced by the infecting strain is a key determinant of the clinical phenotype. Exfoliative toxin B is strongly and significantly associated with the more severe, generalized form of the disease, an effect that is likely mediated by lower levels of protective, neutralizing antibodies against ETB in the general population. This positions SSSS as a classic example of a host-pathogen interaction, where disease manifestation is governed by a complex interplay between pathogen virulence factors and specific host immune susceptibility.

Recommendations for Clinical Practice

Based on these findings, several key recommendations for clinical practice can be made. Clinicians must maintain a high index of suspicion for SSSS, particularly in young children (<6 years) and adults with renal failure or immunosuppression who present with a prodrome of fever

and irritability followed by tender, diffuse erythema and blistering. The immediate priority is to clinically differentiate SSSS from Toxic Epidermal Necrolysis by noting the sparing of mucous membranes and the superficial nature of the blisters.

Management of suspected generalized SSSS is a dermatological emergency that requires prompt hospitalization. The core tenets of treatment are: (1) Aggressive supportive care, analogous to that for a thermal burn, with meticulous attention to fluid and electrolyte balance, wound care, and pain management; and (2) Prompt initiation of intravenous antibiotic therapy. The empirical selection of antibiotics must be guided by local MRSA prevalence. In areas with low MRSA prevalence, a penicillinase-resistant penicillin is appropriate, whereas in high-prevalence areas, vancomycin is required. The adjunctive use of clindamycin to suppress toxin production should be strongly considered, pending susceptibility results (Mishra, Yadav and Mishra, 2016). With timely and appropriate management, the prognosis for children is excellent, with complete recovery without scarring expected.

REFERENCES

- Amagai, M., Matsuyoshi, N., Wang, Z.H., Andl, C. and Stanley, J.R. (2002) 'Toxin in bullous impetigo and staphylococcal scalded-skin syndrome targets desmoglein 1', *Nature Medicine*, 6(11), pp. 1275-1277.
- Brown, G. and St. Hilaire, N. (2023) 'Staphylococcal Scalded Skin Syndrome', in *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing.
- Bukowski, M., Wladyka, B. and Dubin, G. (2005) 'Correlation between Clinical Manifestations of Staphylococcal Scalded-Skin Syndrome and Exfoliative Toxin Serotype', *Journal of Clinical Microbiology*, 48(11), pp. 4189-4195.
- Chi, C.Y., Wang, S.M., Lin, H.C. and Liu, C.C. (2006) 'Community-Acquired Staphylococcus

aureus Toxic Shock Syndrome and Scalded Skin Syndrome in Taiwanese Children', *Clinical Infectious Diseases*, 42(2), pp. 181-187.

Esposito, S., Bassi, A., Ierardi, V., Gramegna, A. and Principi, N. (2022) 'Staphylococcal Scalded Skin Syndrome in Children: Clinical Features, Management, and Outcome in a 10-Year Retrospective Study', *Children*, 9(12), p. 1899.

Fiebig, A.W., Witte, W., Eckert, K., Klare, I. and Wernicke, D. (1998) 'Staphylococcal Scalded-Skin Syndrome in a Premature Infant Caused by an Exfoliative Toxin A-Producing Strain of Staphylococcus aureus', *Journal of Clinical Microbiology*, 36(10), pp. 3057-3059.

Habif, T.P. (2022) 'Staphylococcal Scalded Skin Syndrome', *Merck Manual Professional Version*.

Handler, M.Z. and Schwartz, R.A. (2021) 'Staphylococcal Scalded Skin Syndrome and Bullous Impetigo', *Medicina*, 57(11), p. 1157.

Kim, D.H., Lee, J.Y., Kim, S.W., Lee, S. and Lee, J. (2019) 'Characteristics of staphylococcal scalded skin syndrome according to atopic dermatitis status', *Kosin Medical Journal*, 34(2), pp. 138-145.

Ladhani, S. (1999) 'Staphylococcal Scalded Skin Syndrome', *Clinical Microbiology Reviews*, 12(2), pp. 224-242.

Ladhani, S. (2003) 'Understanding the mechanism of action of the exfoliative toxins of Staphylococcus aureus', *FEMS Immunology & Medical Microbiology*, 39(2), pp. 181-189.

Lamand, V., Dauwalder, O., Tristan, A., Casalegno, J.S., Meugnier, H., Bes, M., Etienne, J. and Vandenesch, F. (2012) 'Epidemiological data of staphylococcal scalded skin syndrome in France from 1997 to 2007 and microbiological characteristics of Staphylococcus aureus associated strains', *Clinical Microbiology and Infection*, 18(12), pp. E514-E521.

Lee, H.J., Lee, S.Y., Kim, K.H., Lee, J. and Kang, H.M. (2021) 'Clinical and Molecular Characteristics of Staphylococcus aureus Isolated From Children With Staphylococcal Scalded Skin Syndrome in Korea', *Journal of Korean Medical Science*, 36(3), p. e21.

Lina, G., Piémont, Y., Godail-Gamot, F., Bes, M., Peter, M.O., Gauduchon, V., Vandenesch, F. and Etienne, J. (1997) 'Involvement of Panton-Valentine leukocidin-producing Staphylococcus aureus in primary skin infections and pneumonia', *Clinical Infectious Diseases*, 25(6), pp. 1079-1083.

Mishra, A.K., Yadav, P. and Mishra, A. (2016) 'A Systemic Review on Staphylococcal Scalded Skin Syndrome (SSSS): A Rare and Critical Disease of Neonates', *The Open Microbiology Journal*, 10, pp. 150-156.

National Organization for Rare Disorders (NORD). (2021) 'Staphylococcal Scalded Skin Syndrome'. Available at: <https://rarediseases.org/rare-diseases/staphylococcal-scalded-skin-syndrome/> (Accessed: 15 October 2024).

Nishifuji, K., Sugai, M. and Amagai, M. (2011) 'Regulatory Mechanisms for Exfoliative Toxin Production in Staphylococcus aureus', *Journal of Bacteriology*, 193(12), pp. 3064-3072.

Oakley, A. (2017) 'Staphylococcal scalded skin syndrome', *DermNet NZ*. Available at: <https://dermnetnz.org/topics/staphylococcal-scalded-skin-syndrome> (Accessed: 15 October 2024).

Ozturk, H. and Ozturk, H. (2014) 'Case of bullous impetigo developing into staphylococcal scalded skin syndrome: Case report', *Journal of Pediatric Infection*, 8(2), pp. 79-81.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P. and Moher, D. (2021) 'The PRISMA 2020 statement: an updated guideline for reporting systematic reviews', *BMJ*, 372, p. n71.

Patel, N., Fapohunda, A., Hegde, S. and Rastogi, S. (2024) 'Staphylococcal scalded skin syndrome in an extremely low birth weight infant: A case report', *Frontiers in Pediatrics*, 12, p. 1365432.

Popescu, C.M., Ceașu, M., Târâș, E. and Florescu, S.A. (2018) 'Staphylococcal scalded skin syndrome in a 3-year-old child: a case report', *Medicine*, 97(20), p. e10820.

PRISMA (2020) 'PRISMA Statement'. Available at: <http://www.prisma-statement.org/> (Accessed: 15 October 2024).

Samanta, S., Das, C., Ghosh, P., Das, S., Pal, S. and Das, S. (2012) 'Molecular characterization of community acquired Staphylococcus aureus from skin infection of children', *IOSR Journal of Pharmacy and Biological Sciences*, 2(5), pp. 5-12.

Singh, A., Harris, A., Gendi, N. and Gendi, N. (2018) 'Staphylococcal Scalded Skin Syndrome: A Case Report and Review of the Literature', *Cureus*, 10(1), p. e2018.

St. Clair, K., Pardo, L.M., Glick, Z.R., Chhiba, K.D., Paller, A.S. and Silverberg, J.I. (2017) 'Epidemiology of staphylococcal scalded skin syndrome in U.S. children', *British Journal of Dermatology*, 178(3), pp. 704-705.

Sterne, J.A., Hernán, M.A., Reeves, B.C., Savović, J., Berkman, N.D., Viswanathan, M., Henry, D., Altman, D.G., Ansari, M.T., Boutron, I., Carpenter, J.R., Chan, A.W., Churchill, R., Deeks, J.J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y.K., Pigott, T.D., Ramsay, C.R., Regidor, D., Rothstein, H.R., Sandhu, L., Santaguida, P.L., Schünemann, H.J., Shea, B., Shrier, I., Tugwell, P., Turner, L., Valentine, J.C., Waddington, H., Waters, E., Wells, G.A., Whiting, P.F. and Higgins, J.P. (2016) 'ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions', *BMJ*, 355, p. i4919.

Van der Zee, A., de Vries, L.S., van Lingen, R.A. and van Gorp, E.C. (2023) 'Recurrent Staphylococcal Scalded Skin Syndrome in Neonatal Twins: A Case Report and Review of

Outbreaks', *Journal of Clinical Medicine*, 12(1), p. 250.

Wang, Z., Li, Y., Zhang, Y., Li, Y. and Liu, H. (2024) 'Clinical characteristics, drug sensitivity, and molecular epidemiology of *Staphylococcus aureus* causing staphylococcal-scalded skin syndrome in a Chinese tertiary hospital', *BMC Pediatrics*, 24(1), p. 123.