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Staphylococcical scalded skin syndrome: a case series description of a rare and critical disease in a tertiary pediatric center

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Abstract

Background Staphylococcal-scalded skin syndrome (SSSS) is a potentially life-threatening disorder characterized by superficial skin blistering caused by exfoliative toxins produced by *Staphylococcus aureus*. This study aimed to investigate SSSS in a cohort of children admitted at a tertiary pediatric hospital in Italy.

Methods Patients discharged with the diagnosis of staphylococcal infection and of SSSS between January 2010 and March 2023 were retrospectively identified using ICD-9-CM codes (695.81 and 041.1, respectively). Medical records were reviewed to extract epidemiological, clinical, and hematological data, treatment details (type and duration), length of hospitalization, and outcomes.

Results Among 971 children with staphylococcal infection, 21 (2.1%) were diagnosed with SSSS. The mean age of 36.8 (interquartile range, IQR 8.5–50.7) months, with 86% under 5 years old. Incidence peaked in winter, summer, and autumn (27.3%, respectively), possibly due to viral co-infection. The admissions/year rate did not indicate an upward trend. Almost all children were healthy. No previous trauma, insect bites, drugs, vaccines, or allergy history have been reported; atopic dermatitis has been reported in one girl. Leukocytosis and elevated C-reactive protein were uncommon. Severe complications were seen in three cases (14.3%): one with severe dehydration with hyponatremia, one with sepsis and the last with Herpes Simplex Virus 1 (HSV1) infection. *S. aureus* was detected by culture from skin lesions in nine cases (42.9%), by real-time polymerase chain reaction (*RT-PCR*) assay on vesicle fluid in seven (33%), and by throat culture in one (4.7%). Drug susceptibility tests ruled out resistance and all children received intravenous (IV) antibiotics: oxacillin in 76% of patients, while teicoplanin and clindamycin in 19%. The median duration of IV and oral antibiotic therapy was 12.8 days (IQR 10–14). Only one patient was treated with IV immunoglobulin. The median hospitalization length was 7.8 days (IQR 5–9). All our cases had a favorable outcome.

Conclusion Demographic, clinical. and hematological features of children with SSSS in this study were comparable with those reported in the literature. The improved awareness of pediatricians should faster diagnosis, which is mainly clinical, and early assessment of appropriate management.

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Background

Staphylococcal scalded skin syndrome (SSSS) is a potentially life-threatening disorder characterized by erythema and superficial skin blistering [1]. It is a toxin-mediated disease caused by exfoliative toxins A (ETA) and B (ETB) produced by certain strains of *Staphylococcus aureus* [2]. Although these toxins act locally on the skin, they may enter the bloodstream and cause a systemic inflammatory response. Therefore, the cutaneous disease may be accompanied by fever and signs of systemic inflammation, either clinical or biochemical.

The condition was first described by Ritter von Rittershain [3] and the term "staphylococcal scalded skin syndrome" was introduced by Melish and Glasgow nearly a century later [4]. Epidemiological data on SSSS remain scarce: in France and Germany, the incidence reported is 0.09 and 0.56 per-million persons per year, respectively [5, 6]; in the US, the annual incidence is 7.67 (range: 1.83–11.88) per-million children, with 45.1 cases per-million infants under 2 years of age [7]. African–American children are less susceptible than Caucasian ones [8, 9]. The condition is most frequently observed in neonates and children under 5 years, with the highest incidence occurring between 2 and 3 years old [1, 10–12]. SSSS can also occur in older children and adults with renal failure, immunologic deficiency, and other chronic illnesses [13–16]. The higher risk in children, especially neonates, may be related to their immature immune system and renal clearance ability [17]. The morbidity rate in young children is high, primarily due to complications such as secondary infections, hypothermia, and dehydration resulting from fluid loss through damaged skin with the consequent electrolyte imbalances [1].

In contrast, the overall mortality rate for SSSS in children is quite low, ranging from 0.3% [18] to 5% [19], unless associated with sepsis or a severe underlying disease.

While most SSSS cases are attributed to methicillin-sensitive *Staphylococcus aureus (MSSA)*, an increase in methicillin-resistant *Staphylococcus aureus* (*MRSA*) has also been recently observed [20, 21]. The syndrome presents as a macular erythema followed by bullous lesions and diffuse epidermal exfoliation. A prodromal localized staphylococcal infection of the skin, throat, nose, mouth, umbilicus, or gastrointestinal tract typically occurs. General malaise, fever, irritability, skin tenderness, and reduced appetite may also be present. Other signs, such as facial oedema, conjunctivitis, and perioral crusting, can also be present. Mucous membranes are typically spared, but dehydration may be a serious complication.

Gentle pressure on apparently normal skin results in the separation of the upper epidermis (Nikolsky's sign) [7]. Complications of SSSS include secondary viral (herpes viruses) or bacterial infections (cellulitis, sepsis, and pneumonia), dehydration, electrolyte imbalance, and hypothermia [22, 23]. Management involves administering anti-staphylococcal antibiotics, fluids, and electrolytes, as well as topically treating the denuded areas [1]. In this study, we aimed to investigate the clinical spectrum of SSSS in a cohort of children admitted to a tertiary pediatric hospital in Italy.

Methods

Study design and population

We retrospectively identified children (aged 0–14 years) with evidence of Staphylococcal infection who were admitted at Meyer Children's Hospital IRCCS, from January 2010 to March 2023.

Inclusion and exclusion criteria

We identified discharges with either a principal or secondary diagnosis of Staphylococcal infection using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code 041.1. Among these, we selected children with a final diagnosis of SSSS (code 695.81). Exclusion criteria were as follows: localized bullous impetigo (BI), bacteremia, endocarditis, osteomyelitis, pneumonia, and septic arthritis.

Data collection

Medical records of the included patients were reviewed to collect the following data:

- demographic data: gender, age, geographic area, and season at onset;
- historical data: familial and personal history, including previous diseases/comorbidities, sport activity and previous hospital admissions;
- clinical features: cutaneous signs, involved areas, Nikolsky's sign positivity, and status of desquamation, as well as systemic symptoms such as fever, pain, weakness, irritability, and loss of appetite;
- clinical types: based on Kang et al. [24], we classified cases into three types: the generalized type was defined as a large area of skin lesions (over 30% of the whole body) with tender erythroderma, large bullae, and a positive Nikolsky's sign; the intermediate type was defined as skin lesions with tender erythroderma, vesicles, or pustules in a regionally limited area (< 30%) and a positive Nikolsky's sign;

the abortive type was defined in case of diffuse scarlatiniform rash with tender erythema without Nikolsky's sign [24];

– complications: severe dehydration with electrolyte imbalance, sepsis, and secondary infections;

– laboratory investigations: C-reactive protein (CRP), white blood cell (WBC) count, procalcitonin (PCT), electrolytes, and immunological parameters (immunoglobulins, dihydrorhodamine testing and lymphocyte subsets), when available;

– microbiological data: detection of *S.aureus* by both standard culture methods and real-time polymerase chain reaction (RT-PCR) assays;

– management: local and systemic therapies (type and duration);

– outcome: length of hospital stay (LOS) and the number of readmissions within two weeks following discharge.

Table 1 Clinical characteristics of 21 children with SSSS

Characteristic		N of cases	%
Demographic data	Male Sex	11	52.4
	Mean age (range), months	36.8 (IQR 8.5–50.7)	
	Season: Autumn	6	27.3
	Winter	6	27.3
	Spring	3	18.1
	Summer	6	27.3
Systemic signs/symptoms	Low appetite	12	57
	Pain	12	57
	Fever	7	33
	Irritability	6	28.6
Clinical signs	Skin erythema	21	100
	Exfoliation/desquamation	21	100
	Skin tenderness	15	71.4
	Facial edema	3	14.2
	Perioral crusting	11	52.4
	Vesicles/ bullae	6	28.6
	Periocular crusting	11	52.4
	Positive Nikolsky's sign	20	95.2
	Perinasal crusting	10	47.6
	Conjunctivitis	8	38
	Mucous membrane involvement	2	9.5
Source of infection	Nares and/or throat	1	4.8
	Skin and/or soft tissue	8	38
	Not reported	12	57
Complications	Sepsis	1	4.8
	HSV1 infection	1	4.8
	severe dehydration	1	4.8
Outcome	Healing	21	100
	Re-admissions	0	0
	LOS, days	7.8 (IQR 5–9)	

Ethical considerations

The study protocol adhered to the ethical guidelines of the 1975 Declaration of Helsinki (6th version, 2008) and was approved by the Institutional Review Board of Meyer Children's Hospital IRCCS.

Statistical analysis

Descriptive statistics (means, IQRs, percentages) were performed to analyse continuous and categorical data. We conducted a univariate logistic regression analysis to assess potential associations between demographic and clinical variables with both the duration of therapy and the length of hospitalization.

Results

Nine hundred seventy-one children with Staphylococcal infection were identified. Twenty-one discharged with the diagnosis of SSSS (21/971, 2.1%) were selected (Table 1). Median age was 36.8 (IQR 8.5–50.7) months, and 86% of children were under 5 years old. Eleven were males (52,4%). Most patients (90.5%) had no underlying condition identified; one patient had a pre-existing cutaneous disease (atopic dermatitis), and one suffered from phenylketonuria. No history of previous trauma, insect bites, drugs, vaccines, or allergy was reported; six children participated in sporting activities. None of the patients had a previous episode of SSSS, or a positive family history of cutaneous diseases. The incidence of SSSS varied by season, with the highest rates occurring in autumn, winter, and summer (27.3%, each). Eight children (38%) presented with respiratory symptoms upon admission. The admissions were evenly distributed throughout the study period (2 cases per year). All patients were admitted to the Pediatric Ward; none required escalation of care to intensive care unit (ICU), and no deaths were reported.

Physical examination revealed varying degrees of cutaneous erythema and superficial desquamation with periorificial, flexural, and/or acral accentuation in all patients. According to Kang's classification [27], the generalized type (Fig. 1) was observed in 13 patients (62.5%), the intermediate in seven (33%), and the abortive type in one (4.5%). Other involvement was noted in eight children: conjunctivitis in seven patients, and oral mucosa involvement in two cases. Systemic symptoms included pain in 11 cases (50%), fever in eight (38%), irritability in six (28%), low appetite in 12 (57%), and pruritus in eight patients (38%).

The diagnosis of SSSS was clinically confirmed in all patients and by the dermatologist in ten cases. One young girl had a skin biopsy performed at local hospital which revealed necrotic keratinocytes with early bullae formation, initially leading to the diagnosis of erythema multiforme. Direct immunofluorescence showed linear deposition of immunoglobulin M and C_3 complement

Fig. 1 Diffuse erythroderma and desquamation in a child with staphylococcal scalded skin syndrome on day 3 after the onset

at the dermo-epidermal junction. Upon transfer to our hospital, the physical examination revealed diffuse skin exfoliation. Clinical assessment by a burn surgeon, dermatologist, and ophthalmologist confirmed the final diagnosis of SSSS, excluding mucosal involvement.

Regarding the laboratory tests, high CRP levels and leucocytosis were observed in 28.6% of cases, eosinophilia in 9.5%, and PCT was always normal. Electrolytes were normal in all patients except one, who had hyponatremic dehydration.

Serum immunoglobulin profile, dihydrorhodamine testing, and lymphocyte subsets, performed in 11 cases, were normal. One patient has antinuclear antibodies (ANA) positivity with a title 1:160, dense, fine speckled pattern. Coeliac disease antibodies were tested in one patient and were negative.

Microbiological findings revealed *S. aureus* in 61.9% of cases. *S. aureus* was detected in cultures from periorificial lesions in nine cases (42.9%), by *RT-PCR* assay on vesicle fluid in seven (33%), and by throat culture in one (4.7%). Panton-Valentine Leucocidin (PVL) was tested in four children and was negative in all cases. No testing for exfoliating toxins was performed in our laboratory.

Sensitivity data for *S. aureus* were available for 10 patients (47%). No isolates were resistant to methicillin, vancomycin, or fusidic acid. Resistance to clindamycin and erythromycin was observed in two isolates.

Five patients had other pathogens isolated by cultures from skin lesions: co-pathogens included *Enterococcus faecalis* in three cases, *Moraxella catarrhalis* in one, and *Streptococcus mitis* associated with *Actinomyces* in another one. In the latter patient, MSSA, *S.*

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Table 2 Univariate analysis of factors associated with duration of therapy

	UNIVARIATE ANALYSIS		
	uOR	CI 95%	*p*
Gender	2,473	0,419; 16,664	0,3949
Age (months)	0,576	0,090; 3,382	0,6699
Community exposure	1,135	0,149; 8,673	1
Siblings	2,62	0,433; 19,045	0,387
Tmax (°C)	1,187	0,200; 7,204	1
Season	1,692	0,283; 10,904	0,6699
Previous hospitalizations	1,118	0,097; 12,916	1
Sports	0,881	0,115; 6,701	1

Table 3 Univariate analysis of factors associated with length of stay

	UNIVARIATE ANALYSIS		
	uOR	CI 95%	*P*
Gender	2,772	0,380; 28,366	0,3615
Age (months)	1,135	0,149; 8,673	1
Community exposure	0,449	0,014; 4,183	0,6227
Siblings	0,681	0,088; 5,202	1
Tmax (°C)	2,772	0,380; 28,366	0,3615
Season	3,63	0,491; 37,847	0,331
Sports	0,727	0,088; 7,707	1

mitis, and *Actinomyces* were cultured also from wound swabs. Blood cultures, obtained from five patients, were negative.

A quantitative *RT-PCR* test on the bloodstream was positive for Human Herpesvirus (HHV) 7 in two patients, HHV 6 in one, Herpes simplex virus 1 (HSV1) in one, and *Escherichia coli* in another child.

Severe complications were seen only in three cases (14.3%): one girl presented severe dehydration with hyponatremia, one had sepsis, and the last had severe HSV1 infection.

All children received IV antibiotics during hospitalization. Only one patient was treated with IV immunoglobulin (1 g/kg). The empiric antimicrobial treatment was oxacillin as the first-line drug in 16 patients, either alone or as part of a combined treatment. Four patients were given clindamycin alone or in combination with other antibiotics, and one patient was given ceftriaxone. The target antimicrobial treatment was oxacillin alone for 10 patients, oxacillin plus another drug (ceftriaxone or clindamycin) for six patients, teicoplanin alone for three patients, and teicoplanin with clindamycin for two cases. Five patients completed the intravenous antibiotic regimen entirely in the hospital. In the remaining 16 cases, therapy was switched to oral antibiotics, including amoxicillin-clavulanate (11 cases), cefixime (1 case), cephalexin (1 case), trimethoprim-sulfamethoxazole combined with rifampicin (1 case), clindamycin plus cefixime (1 case), and amoxicillin-clavulanate combined with rifampicin (1 case). The median length of oral antibiotics was 5.8 days (IQR 5–7). The median duration of IV plus oral antibiotic therapy was 12.8 days (IQR 10–14). In addition to systemic antibiotics, a local treatment with emollients, fusidic acid or mupirocin, eye drops, pain medications, such as acetaminophen, and antihistamine drugs, such as cetirizine or oxatomide, were also prescribed in 76% of cases. All of them received IV fluids. None required enteral tube feeding. No surgical debridement of the skin has been performed.

The median LOS was 7.8 days (IQR 5–9) with a slight difference between boys and girls: the average LOS was 8.2 days for the boys and 7.2 days for the girls.

In the univariate logistic regression (Table 2), none of the assessed variables showed statistically significant associations with the duration of therapy. Although male sex and the presence of siblings appeared to be linked to a longer duration of treatment, these findings did not reach statistical significance. Regarding the univariate analysis for factors associated with the length of hospitalization (Table 3), none of the variable analysed were significantly associated with a longer stay.

All our patients, including those with complications, healed without sequelae and none was re-admitted to our hospital in the following two weeks.

Discussion

S. aureus causes a variety of infectious diseases, ranging from superficial skin infections to severe, toxin-mediated systemic infections. SSSS is a type of systemic disorder mainly caused by coagulase-positive group II *S. aureus* that can cause superficial skin blistering. Skin acantholysis leads to cracks in the epidermis and characteristic skin bullae [25]. The pathophysiologic mechanisms include several steps: first, the production of exfoliative toxins (ETs). Several strains of *Staphylococcus aureus* (Group II) can produce epidermolytic toxins, primarily toxin A (ETA) and toxin B (ETB), which are exfoliative. These toxins have a specific affinity for skin proteins, particularly a skin protein called desmoglein-1 (Dsg-1), a desmosomal cadherin of the superficial epidermis responsible for the adhesion of skin cells (the upper layer of the skin). Thus, the epidermolytic toxins act by binding to Dsg-1 and causing cleavage of the desmosomes, leading to separation between the epidermal cells of the skin. Following the disruption of the desmosomes, epidermal cells detach from one another, causing the formation of blisters, bullae, and peeling of the skin. This process leads to the typical manifestation of skin exfoliation, which may appear like a burn [26].

The diagnosis is clinical and the consultation with a dermatologist should be considered if the diagnosis is

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uncertain. SSSS may resemble other exfoliative skin conditions, such as toxic epidermal necrolysis (TEN), epidermolysis bullosa (EB), Stevens–Johnson syndrome (SJS), toxic shock syndrome (TSS), and pemphigus. Differentiation is primarily based on the presence of mucosal involvement. Bullous impetigo, caused by the localized release of similar toxins, often presents with similar skin findings but is typically confined to specific areas, while SSSS causes a more widespread rash and severe symptoms due to the systemic distribution of these toxins. These conditions may occasionally be mistaken for other disorders that result in superficial blistering [27].

Our retrospective study analysed 21 cases of SSSS from 2010 to 2023 in a tertiary care Children's Hospital IRCCS. SSSS commonly affects neonates and children younger than 5 years, with peak incidence between 2 and 3 years. It is well established that neonates and young children are at greater risk due to their immature immune system, which is unable to neutralize epidermolytic toxins and their limited renal capacity to eliminate these toxins [28, 29]. Similarly, immunocompromised adults or those with renal impairment present a higher incidence [30].

The increased frequency and severity of SSSS in neonates likely results from a combination of factors, including the reduced renal clearance of toxins and the underdeveloped structure of the neonatal epidermis. In addition to age, other predisposing conditions are recognized risk factors for SSSS, particularly in severe cases. These include atopic dermatitis, renal failure, and primary immunodeficiencies [26]. For instance, Hyper-IgE syndrome [31] and Netherton syndrome [32] have been described in children with severe SSSS. In our cohort, none of the patients presented with predisposing conditions, except one child with atopic dermatitis.

A large U.S. study on 589 children with SSSS reported an increase in incidence between 2010 and 2012 compared to 2008–2009 [7]. Similarly, Li et al. observed a rise in incidence Chinese infants, with 79,5% occurring between 2008 and 12 compared to 20,5% between 2004 and 2009 [30]. This upward trend aligns with other previous reports [33, 34]. Conversely, in Europe and regions with high hygiene standards, a decline in SSSS incidence has been noted [6]. In our study, hospital admissions remained stable over time, with an average of two cases per year.

Consistent with the literature [1, 11, 12], most of our patients (86%) were under 5 years years of age, with a slight male predominance as reported in other studies [28, 35]. However, Lyi-Wong [35], found no sex predominance.

Seasonal distribution in our series showed that SSSS was more frequent during winter, autumn, and summer, in line with prior studies [33, 35–37]. Some authors suggest that viral upper respiratory tract (URT) infections,

particularly in autumn, may predispose colonized individuals to SSSS [5]. Previous studies have also documented preceding infections such as URT infections otitis media, conjunctivitis, omphalitis [30], pneumonia [33], pyomyositis [38], and maternal breast abscesses [39]. Similarly, we observed that eight children presented URT symptoms prior to hospitalization.

The clinical course of SSSS is typically characterized by a prodromal phase with fever, irritability, and anorexia. Before the onset of skin lesions, Nikolsky's sign may already be positive. Initial dermatologic findings include widespread erythematous patches and the formation of fragile bullae, which rupture easily, leaving behind denuded, scalded-appearing skin [28, 29, 40]. Exfoliated areas crust over within 24 h, with perioral and periorbital fissures, and complete re-epithelialization generally occurs within two weeks without scarring [4]. In our series, these features were variably present and summarized in Table 1. Based on Kang et al.'s classification [24], the generalized type was most frequent (62.5%), followed by the intermediate type, while the abortive form was rare. Systemic symptoms such as poor appetite and pain were common, while fever and irritability were present in approximately one-third of cases.

In our series, complications occurred in 14.2% of patients and included sepsis, dehydration with hyponatremia, and HSV1 infection. Literature reports that SSSS severity is influenced by toxin burden and the host's immune response. The compromised skin barrier predisposes to secondary infections, hypothermia, and fluid loss. Hence, dehydration and electrolyte imbalances, notably hyponatremia, are frequent complications, underscoring the need for careful fluid management and laboratory monitoring. Interestingly, Blyth et al. reported that fluid overload can paradoxically occur despite hypovolemia being the primary concern [41].

Although rare, other complications include pneumonia and bacteremia (sepsis). Life-threatening events such as toxic shock syndrome [35, 36], acute kidney injury, and thrombosis have also been reported [42].

Regarding laboratory findings, leukocytosis and elevated CRP levels were detected in only 28.6% of cases, indicating a mild or delayed systemic inflammatory response. Consistent with Neubauer et al., laboratory tests (WBC, ESR, CRP) showed limited prognostic value in SSSS management [36]. Zeng et al. demonstrated elevated WBC, CRP, IL-6, and PCT in both bacterial infections and SSSS compared to healthy controls, with PCT levels being notably higher in SSSS [40]. However, in our series, PCT remained negative in all patients, even at onset.

The detection rate of *S.aureus* was high (62%) in our study, which is consistent with prior reports [28, 43]. Blood cultures yielded no significant results, in line with

the low positivity rate typically seen in pediatric populations [5, 33, 35, 44–46] in contrast to adult data [26].

Early diagnosis and timely administration of appropriate parenteral anti-staphylococcal antibiotics, along with supportive care, are crucial. Empirical therapy in our cohort mainly involved oxacillin, alone or in combination, reflecting current recommendations [25, 39]. The ten positive cultures (nine from skin lesions and one from throat swab) all grew MSSA.

In settings with high MRSA prevalence, vancomycin or teicoplanin should be considered upfront, particularly in severe or non-responsive cases [47]. Although no MRSA strains were isolated, six patients required teicoplanin following oxacillin failure, three of whom were critically ill. Additionally, four patients were treated with clindamycin, alone or in combination.

Despite increasing reports of clindamycin resistance [48], resistance was identified in only two isolates (10%) in our study. In contrast, Braunstein et al. reported a clindamycin resistance rate of 52% despite MSSA isolates [47]. Wang et al. also found SSSS-associated strains more frequently resistant to clindamycin but less often resistant to methicillin compared to other S. aureus infections [48].

All patients in our series survived, including those with complications, which aligns with previous studies [35]. This contrasts with larger studies reporting pediatric mortality rates between 0.3% and 5% [4, 6, 40]. In adults, mortality is significantly higher (40-63%) due to underlying comorbidities [28]. Fatal outcomes in children are primarily linked to severe complications such as pneumonia and sepsis [48].

In our cohort, the median length of stay (LOS) was 7.8 days, which is comparable to other studies reporting LOS ranging from 3 to 8 days [35, 48], and even longer among neonates [45]. No readmissions were recorded, consistent with the literature describing recurrence as exceedingly rare [10].

This case series provides insight into the clinical features, management, and outcomes of pediatric SSSS. Early diagnosis and intervention are paramount to reducing morbidity and mortality. Our data suggest a stable incidence in our setting, but results may differ in other geographic areas.

Study limitations include its retrospective design, incomplete data, small sample size, and single-center setting. Furthemore, we lacked data on S. aureus phage types and toxin profiles, limiting etiological characterization. Future studies should be prospective, multicenter investigations incorporating toxin profiling and resistance trends, as well as long-term follow-up to assess recurrence and late sequelae.

Abbreviations

SSSS	Staphylococcal-scalded skin syndrome
IQR	Interquartile range
RT-PCR	Real- time polymerase chain reaction
IV	Intravenous
MSSA	Methicillin-sensitive Staphylococcus aureus
MRSA	Methicillin-resistant Staphylococcus aureus
BI	Bullous impetigo
CRP	C-reactive protein
WBC	White blood cells
PCT	Procalcitonin
LOS	Length of stay
ICU	Intensive care unit
ANA	Antinuclear antibodies
PVL	Panton valentine leucocidin
URT	Upper respiratory tract
HSV1	Herpes simplex virus 1

Declarations

Ethics approval and consent to participate
The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th version, 2008). The study protocol was approved by the Institutional Review Board of Meyer Children's Hospital IRCCS.

Consent to publication
Written informed consent for data publication was obtained from the parents of enrolled children.

Competing interests
The authors have no relevant financial or non-financial interests to disclose.

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