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Stevens-Johnson syndrome and toxic epidermal necrolysis in children: A case series and review of the literature

Stevens-Johnsonov sindrom in toksična epidermalna nekroliza pri otrocih: prikaz primerov in pregled literature

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Abstract

Stevens-Johnson syndrome and toxic epidermal necrolysis are rare life-threatening diseases that manifest with bullae formation and denudation of the skin and mucosa. They are most often a consequence of an immune-mediated drug reaction, rarely due to other causes. After discontinuation of the culprit drug and treatment of bacterial infection, if proven as a cause of the disease, local eye, skin, and mucosal therapy are prescribed. The drugs most often used in the systemic treatment are glucocorticosteroids (GCS) and intravenous immunoglobulins (IVIG). The cooperation between various specialists is of crucial importance.

We present a case series of patients treated at the Department of Alergology, Rheumatology and Clinical Immunology, University Children's Hospital Ljubljana, Slovenia, and a review of the literature. From 2011 – 2019 we treated six children with SJS/TEN. In four children the disease was associated with a drug, in one child with infection with *Mycoplasma pneumoniae* and in one child the cause of the disease was not identified. Four children were treated with GCS and IVIG, the child with *Mycoplasma pneumoniae* infection was treated with azithromycin and IVIG, one child was treated only with local therapy. The outcome of the disease was good in all patients, without late sequelae.

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Izvleček

Stevens-Johnsonov sindrom (SJS) in toksična epidermalna nekroliza (TEN) sta redki življenje ogrožajoči bolezni, ki se kažeta z nastajanjem mehurjev ter odstopanjem povrhnjice kože in sluznic. Najpogosteje sta posledica imunsko sprožene reakcije na zdravilo, redkeje zaradi drugih vzrokov. Poleg prekinitve zdravljenja z zdravilom, ki je lahko sprožilo SJS/TEN, ali uvedbe zdravljenja bakterijske okužbe, če je ta kot vzročni dejavnik dokazana, uvedemo lokalno zdravljenje sprememb na očeh, koži in sluznicah, v težjih primerih pa še sistemsko zdravljenje z glukokortikosteroidi (GKS) in/ali intravenskimi imunoglobulini (IVIG). Za optimalni izid bolezni je bistveno sodelovanje med specialisti različnih strok.

Prispevek predstavi skupino bolnikov, obravnavanih na Kliničnem oddelku za otroško alergologijo, revmatologijo in klinično imunologijo Pediatrične klinike UKC v Ljubljani in pregled literature. V letih 2011–2019 smo zdravili šest otrok s SJS/TEN. Pri štirih otrocih je bil sprožilni dejavnik zdravilo, pri enem okužba z *Mycoplasmo pneumonie*, pri enem bolniku pa etiologije nismo mogli opredeliti. Z GKS in IVIG so bili zdravljeni štirje otroci, en otrok z okužbo z *M. pneumonie* je bil zdravljen z azitromicinom in IVIG, en otrok pa je prejel le zdravila lokalno. Izid bolezni je bil pri vseh otrocih dober, in sicer tudi brez poznih posledic bolezni.

1 Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are characterized by a macular rash with bullae, areas of epidermal detachment and mucosal involvement at two or more sites. The designations SJS and TEN are considered a disease continuum with SJS at one end of the spectrum with epidermal detachment limited to less than 10% of the body surface area and TEN at the other with epidermal detachment of more than 30% of the body surface area. The SJS/TEN overlap syndrome denotes the disease form with epidermal detachment of 10–30% of the body surface area (1). In the past, SJS and TEN were classified in the same disease spectrum as erythema multiforme (EM). On the basis of new descriptive classifications published in 1993, it is only in recent years that the view that these are separate diseases has prevailed in the professional public. The division is important as the triggers, disease course and treatment differ and misdiagnosis can lead to either insufficient treatment or overtreatment (Table 1) (2). The most common triggers are drugs and infections (3-7).

The disease pathogenesis is not fully understood. Cytotoxic T lymphocytes (CLT) and natural killer cells (NK) induce keratinocyte apoptosis in the basal skin and mucosal layers with subsequent bullae formation and epidermal detachment through the secretion of cytotoxic molecules, particularly granulysin and cytokine IL-15 (8-11). Treatment with sulfonamides, carbamazepine, oxicam and allopurinol increases the risk of the disease if the patient is a carrier of a certain HLA allele, particularly group A and B (12).

The diagnosis is clinical. The disease begins with nonspecific prodromal symptoms, which are followed in a few days by mucosal involvement at two or more

Table 1: Classification of erythema multiforme (EM) and overlap of Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). Partially adapted from Bastuji Garin (2).

Classification	EM	EMM	SJS	SJS/TEN	TEN
Epidermal detachment	No	< 10%	< 10%	10 –30%	> 30%
Typical target lesions	Yes	Yes	Yes	Yes	Yes
Atypical target lesions	Raised	Raised	Flat	Flat	Flat
Maculae	No	No	Yes	Yes	Yes/no
Mucosal involvement	No	Yes	Yes	Yes	Yes

Legend: EM – erythema multiforme; EMM – erythema multiforme major; SJS – Stevens-Johnson syndrome; SJS/TEN – SJS and TEN overlap; TEN – toxic epidermal necrolysi.

sites and a characteristic rash with bullae and epidermal detachment (2,6,13,14). Due to the detachment of large areas of skin and mucosal involvement, secondary bacterial infections and other complications occur, prompting the need for additional medical procedures (13). The eyes are commonly affected along with the skin, but ocular involvement can be the first sign of the disease (15). Common long-term sequelae include cutaneous and ocular complications (8,13). In the differential diagnosis, SJS and TEN should be distinguished from EM and other bullous cutaneous diseases. SJS and EM can be differentiated on the basis of the characteristic typical target lesions and atypical raised target lesions, which do not occur in SJS (1,12).

Prompt discontinuation of the causative drug is crucial in treatment. The disease on average reaches the peak in severity after eight days from the onset of symptoms. Afterwards, as long as the exposure to the drug has ceased, the clinical presentation begins to improve (1). If the disease was caused by a bacterial infection, antibiotic treatment is required. In addition to local treatment, systemic treatment can be initiated in severe cases with glucocorticosteroids (GCS) and rarely with intravenous immunoglobulins (IVIG) or other immunomodulatory drugs (5,7).

2 Methods

In the information system of the University Children's Hospital in Ljubljana (UCHL) we searched for patients with a discharge diagnosis of SJS or TEN who were treated at the Department of Allergology, Rheumatology and Clinical Immunology from 2011 to 2019. We re-examined their documentation to confirm the diagnosis. We collected data on age at diagnosis, clinical presentation, disease trigger, treatment, course, and disease outcome. The study was approved by the Republic of Slovenia National Medical Ethics Committee (number 0120-446/2019/10, on 15. 10. 2019).

3 Results

From 2011 to 2019, six children with SJS and TEN were treated at the Department of Allergology, Rheumatology and Clinical Immunology. One child had SJS/TEN and five had SJS. The average age was 10 years (2–17 years). Prior to disease onset, three children were taking one drug and two children took several drugs; in one child, no prior drug use was reported.

In Table 2, we present our patients, possible SJS/TEN triggers and systemic treatment they received. In

Table 2: Patient description.

	Sex	Age (years)	H	T	Possible trigger	Treatment	Complications
1.	F	15	17	1	Penicillin V, Paracetamol, Naproxen, Ayurvedic gel.	IVIG GCS	Secondary skin infection with *S. aureus*. Eyelash loss.
2.	M	2.5	18	26	Oxcarbazepine.	IVIG GCS	
3.	M	6.5	10	10	Oxcarbazepine, Diclofenac, Ibuprofen, EBV infection.	IVIG GCS	Pleural effusion. Dyspnoea.
4.	M	12	8	8	*M. pneumonie.*	Azithromycin IVIG	No complications.
5.	M	5.5	15	/	Paracetamol, infection?	IVIG GCS	No complications.
6.	F	17.5	3	6	Trimethoprim, sulfamethoxazole.	No specific treatment	No complications.

Legend: F – female sex; M – male sex; H – duration of hospitalization in days; T – the time from the start of the drug/infection to the appearance of bullae in days; / – unknown; *S. aureus* – *Staphylococcus aureus*; EBV – *Epstein Barr virus*; *M. pneumonie* – *Mycoplasma pneumonie*.

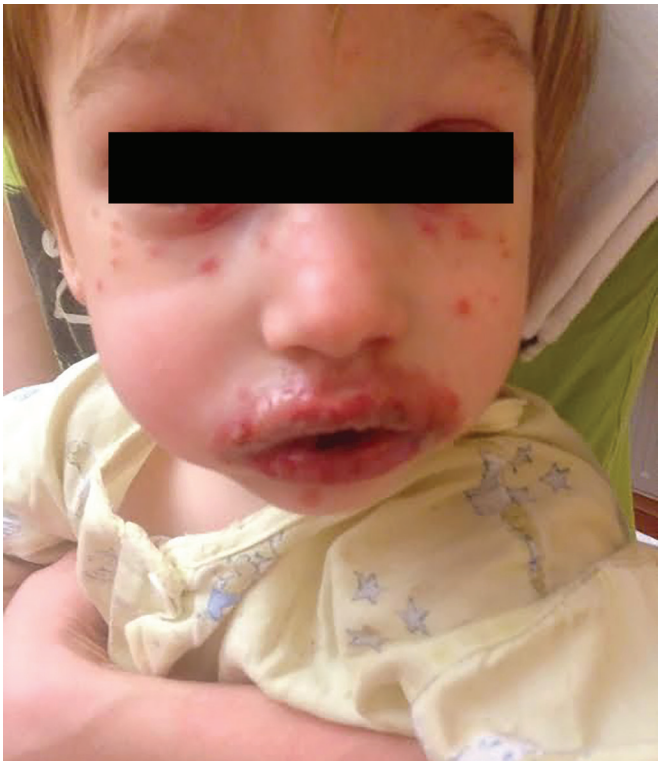

Figure 1: Bullae, detachment of the lip epidermis and smaller bullae around the eyes.

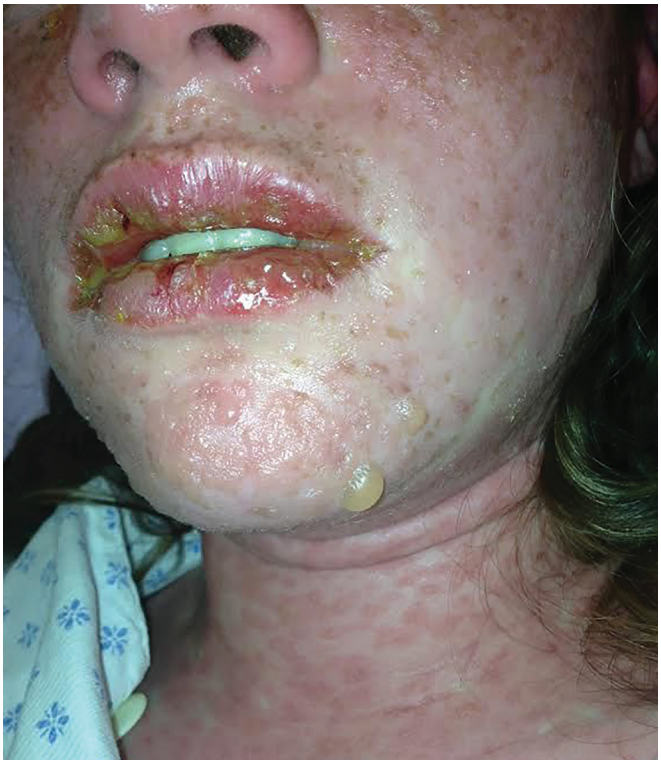

Figure 2: Detachment of the lip epidermis, bullae on the chin, diffuse macular rash.

one patient, the cause could not be identified as the immune reaction could have been caused by an infection or paracetamol. Bullous cutaneous lesions appeared on average 10.2 days after exposure to the trigger (1–27 days) and in two patients who took oxcarbazepine after 18.5 days on average (10 and 27 days). In one patient, concurrent acute infection with the Epstein Barr virus (EBV) was present. The average length of hospitalization was 11.8 days (3–18 days).

3.1 Clinical presentation

In all patients, bullous cutaneous lesions of varying degrees were present; the oral mucosa was also affected in all patients (Figure 1–3). Mucopurulent conjunctivitis was diagnosed in five patients, conjunctival hyperaemia was present in one patient, and none of the patients had corneal lesions. Inflammation of the genital mucosa was found in three patients. Hepatosplenomegaly, difficulty breathing and pleural effusion on chest radiograph were present in a patient who was recovering form a concurrent EBV infection. A patient with SJS/TEN developed a secondary skin infection with *Staphylococcus aureus* (*S. aureus*).

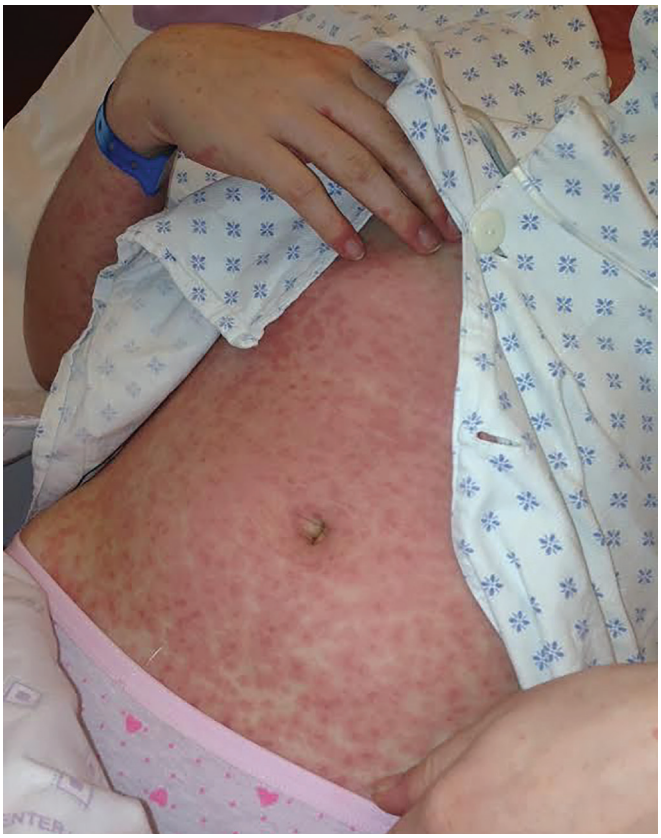

Figure 3: Characteristic skin rash - macules with purpura at the centre.

3.2 Laboratory results

Leukocyte and haemoglobin values were within the age range in all patients. C-reactive protein (CRP) and sedimentation rate (SR) were slightly elevated in five patients, SR on average 29.8 mm/h (14-52 mm/h), CRP on average 51.9 mg/L (3.8–82 mg/L). Elevated liver enzymes were observed in two patients, one of whom had a concurrent EBV infection.

3.3 Treatment

In all patients, treatment with any possible triggering drug was discontinued immediately after admission. In one, the drug was discontinued the day before the onset of SJS symptoms due to ineffectiveness. Five patients were treated with a single dose of IVIG, four at a dose of 1 g/kg and one at a dose of 0.5 g/kg. Three patients received IVIG one day after the onset of bullous lesions, two received IVIG when mucosal involvement was detected one day before the onset of cutaneous lesions. Four were also treated with systemic GCS, which they received on average one day after the onset of bullous cutaneous lesions (three intravenously at a dose of 10 mg/ kg, one at an oral dose of 1 mg/kg). A patient with *M. pneumoniae* infection received azithromycin intravenously.

The treatment was carried out in cooperation with specialists from other disciplines; dermatologists, ophthalmologists, a dental specialist and, in one case, a plastic and reconstructive surgery specialist took part in the treatment. All patients received appropriate supportive care to maintain fluid and electrolyte homeostasis, along with analgesics and medical care to prevent secondary bacterial infections and mucosal complications. Five required total parenteral nutrition (TPN); one required intravenous fluid replacement. One with SJS/TEN needed morphine for pain relief. In all patients, attention was paid to possible secondary bacterial infection. One patient with SJS/TEN was treated with intravenous flucloxacillin due to a secondary skin infection with *S. aureus*. Prophylactic systemic antibiotic treatment is not indicated and our patients have not received it. An essential part of treatment was local treatment of cutaneous and mucosal lesions. We performed skin care with antibiotic and corticosteroid ointments and ophthalmic therapy with saline rinses, artificial tears, antibiotic and corticosteroid drops and ointments. In all patients, photobiomodulation with a low-level laser was performed to facilitate faster recovery of the oral mucosa and relief of oral pain. Additionally, oral mucosal care with triamcinolone and lidocaine was performed.

3.4 Complications and long-term outcome

None of our patients needed treatment in the intensive care unit. Complications included secondary bacterial skin infection in one patient and pleural effusion in another. Long-term skin or eye sequelae were not observed.

4 Discussion

SJS and TEN are rare diseases. In the last four years, five studies were published, involving mainly smaller groups of children (5,16-20). The largest multi-centric study, published in 2018, included data on 898 patients from 47 US centres over a 7-year period. This study mainly describes the treatment and outcome of the disease, but does not contain data on disease triggers (16). Data from recent research are presented in Table 3.

In the last nine years, we treated six children with SJS or TEN at the Department of Allergology, Rheumatology and Clinical Immunology at UCHL. It is possible that patients with a milder clinical presentation were treated elsewhere. The number of boys with SJS/TEN in our cohort was higher compared to the number of affected girls (2:1). The yearly incidence of SJS and TEN is estimated at 1.4-5.7/million; it is higher in children under 10 years of age and in adults over the age of 80 (21,22). There are no epidemiological data for Slovenia. In patients who were treated at UCHL, the disease was triggered by a drug in four cases (66%). In the one patient in whom the trigger could not be fully identified, the possible trigger was a drug. In three patients, the trigger was a high-risk drug for SJS/TEN.

The most common trigger of SJS/TEN are drugs, in 65-57% of adults (3). In children, a drug is a slightly less common trigger at approximately 53% (4). However, in some recent studies, only children in whom the disease was triggered by a drug were included (5,18,20). In patients in whom a drug was the trigger, a high-risk drug was the trigger in 43–48% (3). According to the findings of the European study of severe cutaneous adverse reactions (EuroSCAR), the risk of developing SJS/TEN is highest in sulfamethoxazole and trimethoprim, other sulfonamide antibiotics, carbamazepine, phenytoin, nevirapine, phenobarbital, lamotrigine and allopurinol. The risk is significantly higher when taking non-steroidal anti-inflammatory drugs (NSAID) with acetic acid (diclofenac, indomethacin), macrolides, quinolones,

Table 3: Data collected from recent studies after 2016 (comparison of triggers, treatment and outcome of overlap of Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) in children.

Author	Sibbald et al. (18)	Antoon et al. (16)	Sato et al. (17)	Chatproedprai et al. (19)	Techasatian et al. (5)	Cekic et al. (20)
Country / year of publication	USA / 2020	USA / 2018	Japan / 2018	Thailand / 2018	Thailand / 2018	Turkey 2016
Data collection period	2008–2018	2008–2015	2000–2015	1997–2016	1992– 2012	2010– 2015
Type of study	R, E	R, M	R, O	R, O	R, O	R, O
Nr. of included patients	16	898	15	36	30	11
Age (years)	2–19	0–18	1–15	0–18	0–18	2–15
Proportion of SJS SJS /TEN TEN	No data	86.2% No data 13.8%	80% No data 20%	55% 11% 33%	80% No data 20%	18% 36% 46%
Infectious trigger Number (%)	No data	No data	6 (40%)	4 (11%)	-	2 (18%)
Drug trigger Number (%) Antiepileptics Antibiotics	16 (100%) 5 (31%) 9 (56%)	No data	8 (60%) 1 (6%) 3 (20%)	26 (72%) 13 (36%) 9 (25%)	30 (100%) 18 (60%) 8 (27%)	11 (100%) 5 (45%) 4 (36%)
Treatment: Local treatment, GCS, IVIG, GCS + IVIG, Antibiotics, Antiviral drugs, Other.	2 (12%) 1 (6%) 8 (50%) 4 (25%) - - Etanercept (1 case)	18% 25% 17% 60% 23% -	2 (13%) 8 (53%) / 4 (26%) 11 (73%) - Plasmapheresis + cyclosporine (1 case)	8 (22%) 24 (66%) 1 3 - - -	29 (96%) 1 (3%) - - - -	Cyclosporine (1 case)
Duration of hospitalization	No data	Median 8 days	Median 29 days	9.9 days on average	14 days on average	No data
ICU admission MV	No data	23% 9%	No data	No data	2 (6%)	No data
Mortality rate SJS TEN	No data	0. 6% 0.1% 3.2%	No data	No data	6% 6%	No data
Long-term sequelae	4 (25%) – eyes 3 (19%) – loss of skin pigmentation	No data	1 (6%) – obliterative bronchiolitis	4 (11%) – eyes	4 (13U) – eyes	No data

Legend: R – retrospective study; O – one centre participating – monocentric study; M – multicentric study; GCS – systemic glucocorticosteroids; IVIG – intravenous immunoglobulins; ICU – intensive care unit; MV – mechanical ventilation; SJS – Stevens-Johnson syndrome; SJS/TEN – SJS and TEN overlap; TEN – toxic epidermal necrolysi.

cephalosporins, tetracyclines, aminopenicillins and sertraline. Pantoprazole can also trigger SJS and TEN (3). In children, the risk of SJS/TEN was increased with antiepileptics and antibiotics (Table 3). In 85-100% of patients taking high-risk drugs, the reaction developed less than eight weeks after starting the drug, the median time delay was 15-24 days, and in children 10 days for all groups of drugs, longer for antiepileptic drugs and less, usually 1-4 days, when taking paracetamol (3,5). It is more likely that the reaction is caused by a particular drug if it occurs within the described time frame and the patient is not taking other high-risk drugs at the same time.

The second most common reason for SJS and TEN are infections (6). In our group of patients, infection was proved in only one case, namely the *M. pneumoniae* infection. In one patient, the cause could not be determined with certainty, which is comparable to larger epidemiological studies (4,7).

In some studies, infections are more likely to trigger disease in children than in adults. In a study by Finkelstein et al, the cause was *M. pneumoniae* infection in 22% of cases and herpes simplex virus (HSV) infection in 9% (7). Less common causes of SJS or TEN are human immunodeficiency virus (HIV) infection, malignancy, vaccination, systemic diseases, and food (6). In about 18% of cases, a clear trigger cannot be found (7). In 18% of patients, the disease may recur, so it is important to identify the trigger. Lifelong avoidance of the trigger is necessary, but the potential trigger should not be identified by provocation (7). The patient who had SJS after sulfamethoxazole and trimethoprim had previously had a mild clinical presentation with oral ulcers while taking the same drug. In assessing the possible trigger, we rely primarily on anamnestic data and epidemiological research on disease triggers. In some cases, additional investigations may be carried out. In the patient who developed SJS/TEN after taking paracetamol, naproxen and penicillin, paracetamol would be the most likely trigger, based on epidemiological studies and time frame, but she tested positive for lymphocyte activation (LAT) when tested with penicillin V. The patient also had positive skin tests for cephalosporins and meropenem.

In our patients, the diagnosis was clinical with a clinical presentation consistent with the descriptions in the literature in all patients. Five patients had a fever above 38°C. All patients had involvement of the oral mucosa and conjunctivae and three of the genital mucosae (vulvitis was present in one patient, balanitis in two).

The duration of hospitalization in our study was comparable to the duration of hospitalization in other studies. In a Thai study, the duration of hospitalization was 12.3 days in patients with SJS and 20 days in patients with TEN; in the EuroSCAR study, the duration of hospitalization was 17 days for SJS and TEN (4,5) (Table 3).

Research on the systemic treatment of children with SJS/TEN is rare, and the results differ in different studies. Data from recent studies are collected in Table 3.

In our group of patients, five children were treated with IVIG and four additionally with GCS with good results without long-term sequelae. The clinical presentation was the mildest and duration of hospitalization was shortest in the girl whose trigger drug was discontinued before the onset of SJS symptoms. This confirms the importance of stopping treatment with a trigger immediately. The fact that we started treatment early in the course of the disease, mostly on the day bullous lesions appeared, probably contributed to the good outcome in our patients.

A larger meta-analysis by Zimmerman et al reported on better survival of patients, treated with GCS, in three included studies, but the difference was statistically significant in only one of these studies. In this meta-analysis, the results of treatment with cyclosporine were promising, but treatment with other immunomodulatory drugs (including IVIG) was not beneficial (23). A study by Techasatian et al, in which 30 children were included, proved that early treatment with GCS in children shortened the duration of hospitalization (5). In a newer study with 16 children, 75% of them were treated with IVIG; 50% received only IVIG and 25% received additional GCS. Additionally, one child required the TNF alpha inhibitor etanercept (18). In the discussion, the authors conclude that treatment with IVIG and steroids is likely to be a good combination in patients with SJS and TEN, but there is currently insufficient data to recommend such treatment in all cases. Several case reports have been published, describing the beneficial effects of other immunomodulatory drugs such as cyclosporine, rituximab and etanercept (24-26). In 2019, British recommendations for the treatment of SJS/TEN were issued, which recommend that the decision on immunomodulatory treatment should be individual (14).

In our patients, long-term ophthalmic sequelae were not detected. We detected a secondary bacterial skin infection with *S. aureus*. Two patients had elevated liver enzymes (one of these patients had a concurrent EBV infection). One patient had difficulty breathing

Table 4: Local treatment.

Skin	Oral mucosa	Eyes	Genital mucosa
• Saline gauze dressing • Silicone mesh for wounds • 0.05% betamethasone with 0.1% gentamicin for wounds twice daily • 0.05% alclometasone ointment for erythematous facial lesions twice daily • 0.05% betamethasone ointment for erythematous body lesions without wounds twice daily • Fish ointment • 30% water in Eucerol • Cooling ointment	• Photobiomodulation with low-level laser • 0.1% triamicinolone in Orobase three times daily • 3% oxytetracyclines in Orobase three times daily • 1% lidocaine in Orobase three times daily • 2% miconazole oral gel four times daily Lips • Gentamicin ointment • Antiseptic cream three to five times daily • Fish ointment	• Rinses with normal saline or artificial tears without preservatives six times daily • 0.1% dexamethasone (or 0.1% dexamethasone with neomycin and polymyxin B) eye drops* three to four times daily • Chloramphenicol eye ointment three times a day • Vitamin eye ointment • Carbomer eye gel before sleep	• 2% clotrimazole as a vaginal cream twice daily • Antiseptic cream three to five times daily

Legend: * Corticosteroid eye drops can only be prescribed by an ophthalmologist.

and a pleural effusion. Of the long-term sequelae, ophthalmic complications are most commonly described in the literature, such as dry eye, corneal scarring, keratopathy and subconjunctival fibrosis (5,18,19). All our patients recovered. The mortality rate of SJS or TEN is 22% and is higher in TEN (3). Paediatric mortality is lower and has been estimated at 7.5% in SJS and TEN; 0.35% in SJS and 2-33% in TEN (1,5,7,16). The most common cause of death is septic complications. For a good outcome of treatment, a multidisciplinary approach and involvement of specialists of different subspecialties of dermatology, ophthalmology, paediatric and preventive dentistry and, if required, urology and gynaecology is required (13). The team approach to treatment, which included physicians of several specialities, enabled the rapid initiation of all systemic and local drugs and non-pharmacological measures, including local cutaneous and mucosal treatment, which in our opinion significantly contributed to the excellent disease outcome in all patients without late sequelae. In Table 4, we present the local treatment used in our patients, which was the result of a team effort by subspecialists in several fields and represents the current recommendations for the local treatment of children with SJS/TEN in Slovenia.

5 Conclusion

SJS/TEN are very rare diseases, so it is of particular importance that the treatment of severe paediatric cases is carried out in an institution with access to specialists in different fields. The timely clinical recognition of the disease and discontinuation or treatment of the trigger are key to a good treatment outcome, in which, in addition to local treatment, rapid initiation of appropriate systemic treatment in patients with severe disease is necessary. In this article, for the first time in Slovenia, we presented the approach to the treatment of children with SJS/TEN.

Conflict of interest

None declared.

Parental consent for publication

The children's parents agree with the publication of the article describing their cases.

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