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Severe cutaneous adverse drug reactions: incidence, clinical characteristics, treatment, and outcome in pediatric patients

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Abstract

Background: Severe cutaneous adverse drug reactions (SCARs) can cause significant morbidity and mortality. Clinical data regarding such conditions is still limited in the pediatric population.

Objective: To investigate the incidence, clinical characteristics, treatment, and outcome of SCARs in Thai pediatric patients.

Methods: This retrospective study enrolled 52 patients aged less than 18 years who were diagnosed with acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or SJS/TEN overlap during January 2005 to August 2021 at Siriraj Hospital.

Results: SCARs were slightly more prevalent in females than in males (51.9% vs. 48.1%). Median age at diagnosis was 97 months, and median length of hospital stay was 11 days. DRESS, SJS, TEN, AGEP, and SJS/TEN overlap was found in 44.2%, 36.5%, 9.6%, 5.8%, and 3.8%, respectively. The most common etiologies were antimicrobial agents (40.3%) and anticonvulsants (35.5%). Target lesions, vesicobullous lesions, purpura, positive Nikolsky's sign, and skin tenderness were significant in blistering SCARs. Hematologic (84.6%) and hepatic (65.5%) manifestations were common. Treatment varied according to the clinical features of each condition. Systemic corticosteroids showed some benefit in SJS/TEN. One patient diagnosed with TEN died for an overall SCARs mortality rate of 1.9%.

Conclusion: The unique characteristics of SCARs described herein can lead to timely and accurate diagnosis and proper management.

Key words: Acute generalized exanthematous pustulosis, drug hypersensitivity, drug reaction with eosinophilia and systemic symptoms, pediatric drug reactions, SCARs, severe cutaneous drug reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis

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Introduction

Severe cutaneous adverse drug reactions (SCARs) are potentially lethal drug reactions that manifest primarily dermatologically, but internal organ involvement is also observed in most cases. SCARs are classified into the following 5 clinical subtypes: acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN overlap.

The overall incidence of adverse drug reactions in hospitalized children was reported to range from 4.3-16.7%, and 4.7-12.3% of those reactions were regarded as being severe.[1,2]

Each of the 5 different types of SCARs has a distinct etiology and pathogenesis. A multicenter study by Misirlioglu, et al. found SJS/TEN to be the most common type of SCARs followed by DRESS and AGEP respectively. Antibiotics and antiepileptic drugs were the two most common causes. Infectious etiology was found in SJS/TEN. Mortality rate was 2.9% in SJS/TEN, which was lower than in adult.[3]

As the incidence of SCARs increases and the diseases are associated with high disease burden,[2] enhanced understanding will lead to better care and outcomes. Data specific to SCARs in pediatric population worldwide, including Thailand, are scarce. Accordingly, the aim of this study was to investigate the incidence, clinical characteristics, treatment, and outcome of SCARs in Thai pediatric patients.

Methods

Study design and subjects

This retrospective descriptive study enrolled patients aged less than 18 years who were diagnosed with AGEP, DRESS, SJS, TEN, or SJS/TEN overlap at the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during the January 2005 to August 2021 study period. Electronic medical records were used as the data source, and the following patient data were collected: demographic data, clinical manifestations, laboratory investigations, treatment, and outcome. SCARs diagnoses were identified using International Classification of Diseases (ICD) 10th revision (ICD-10) diagnostic codes. All SCARs diagnoses were made by pediatric dermatologists during admission. AGEP, SJS, TEN, and SJS/TEN overlap were diagnosed clinically. Diagnosis of DRESS was made using RegiSCAR score and Japan equivalent criteria. Patients with incomplete data in the medical records were excluded from the study. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si768/2021).

Statistical analysis

PASW Statistics version 18 (SPSS, Inc., Chicago, IL, USA) was used to analyze the data. Descriptive data are presented as number and percentage for categorical data, mean ± standard deviation (SD) for normally distributed continuous data, and as median and interquartile range (IQR) for non-normally distributed continuous data. Independent samples *t*-test or one-way analysis of variance (ANOVA) was used to compare ordinal variables, and chi-square test or Fisher's exact test was used to compare nominal variables. Relationship between two ordinal factors was analyzed with Pearson's correlation test. All tests were regarded as statistically significant at a *p*-value of less than or equal to 0.05.

Results

SCARs were reported in 62 of the 211,700 pediatric patients admitted to our center during the 2005-2021 study period for an annual SCARs incidence of 17.6 cases per million inpatients. However, 10 of those 62 patients were excluded due to having incomplete data. The remaining 52 patients were enrolled, and their data were included in the final analysis. Patient demographic data are shown in **Table 1**. Females were slightly more likely to develop SCARs than males (51.9% vs. 48.1%, respectively). The median age at diagnosis was 97 months (IQR: 48-153).

Table 1. Demographic and clinical characteristics of the 52 included SCARs patients.

Characteristics	Values
Gender, n (%)	
- Female	27 (51.9%)
- Male	25 (48.1%)
Age at diagnosis of SCARs (months), median (IQR)	97 (48.0-153.0)
Length of hospital stay (days), median (IQR)	11 (8.0-28.0)
- DRESS	25 (10.0-53.0)
- SJS	8 (5.5-13.3)
- TEN	16 (10.0-117.0)
- AGEP	3 (N/A)
- SJS/TEN overlap	10 (N/A)
- Overall SJS/TEN	9 (6.5-16.5)
Clinical subtype of SCARs, n (%)	
- DRESS	23 (44.2%)
- SJS	19 (36.5%)
- TEN	5 (9.6%)
- AGEP	3 (5.8%)
- SJS/TEN overlap	2 (3.9%)
Previous type I drug hypersensitivity, n (%)	
- Urticaria and/or angioedema	3 (5.8%)
- Anaphylaxis	2 (3.8%)
Underlying disease, n (%)	
- Epilepsy	18 (35.6%)
- Malignancy	4 (7.7%)
- Chronic infection	3 (5.8%)
- Others	12 (23.1%)

Abbreviations: SCARs, severe cutaneous drug adverse reactions; IQR, interquartile range; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; AGEP, acute generalized exanthematous pustulosis; SJS/TEN overlap, Stevens-Johnson syndrome/toxic epidermal necrolysis overlap; N/A; not available

The length of hospital stay varied widely with a median of 11 days (IQR: 8-28). The incidence of the different types of SCARs was, as follows: DRESS (n = 23, 44.2%), SJS (n = 19, 36.5%), TEN (n = 5, 9.6%), AGEP (n = 3, 5.8%), and SJS/TEN overlap (n = 2, 3.8%). Five cases (9.6%) had previous type I drug hypersensitivity, which was anaphylaxis and/or urticaria. None had a previous type IV drug hypersensitivity reaction. No family history of drug allergy was noted for any patient. Underlying medical conditions were found in 71.1% of subjects. Of those, epilepsy (35.6%) and malignancy (7.7%) were the most prevalent. Other conditions included chronic infection, thalassemia, and cyanotic heart disease. Twenty-seven patients (51.9%) were admitted due to SCARs, whereas the rest were admitted due to other causes and developed SCARs during hospitalization.

Using the causality assessment approach, a single culprit was implicated in 43 cases, and multiple plausible etiologies were suspected in 8 individuals. Overall, 61 possible causes were identified. A summary of the etiology of SCARs and the latency period compared among the 5 types are shown in **Table 2**. The most common culprits were medication (n = 57, 93.4%) and infection (n = 2, 3.3%). Two cases (3.3%) were concluded to be idiopathic. The mean latency period was longest in TEN (22.2 ± 22.4 days), and shortest in AGEP (1.7 ± 1.2 days).

The majority of the identified medications were antimicrobial agents (41.0%) and anticonvulsants (37.7%). Phenobarbital (18.0%) was the most prevalent drug, followed by phenytoin (13.1%) and sulfonamides (9.8%).

The clinical signs are summarized in **Table 3**. Tachycardia (61.5%), fever (69.2%), and tachypnea (51.9%) were common. In DRESS patients, hepatomegaly (47.8%) and lymphadenopathy (39.1%) were also commonly reported. Development of hepatomegaly differed among the 5 SCARs subgroups with the highest observed incidence in DRESS (p = 0.014).

Table 2. Etiology and latency period compared among the 5 different types of severe cutaneous adverse drug reaction evaluated in this study.

Variables	AGEP (n = 3)	DRESS (n = 30)	SJS (n = 19)	SJS/TEN overlap (n = 2)	TEN (n = 5)	Total (N = 61)†
Medication						
Antimicrobials	2 (40.0%)	16 (53.3%)	5 (26.3%)	1 (50.0%)	1 (20.0%)	25 (41.0%)
- Sulfonamides	1 (20.0%)	3 (10%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	6 (9.8%)
- Carbapenems	1 (20.0%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (8.2%)
- Penicillins	0 (0.0%)	3 (10.0%)	1 (5.3%)	1 (50.0%)	0 (0.0%)	5 (8.2%)
- Cephalosporins	0 (0.0%)	2 (6.6%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	4 (6.6%)
- Others	0 (0.0%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	5 (8.2%)
Anticonvulsants	0 (0.0%)	12 (40.0%)	7 (36.8%)	1 (50.0%)	3 (60.0%)	23 (37.7%)
- Phenobarbital	0 (0.0%)	7 (23.3%)	1 (5.3%)	1 (50.0%)	2 (40.0%)	9 (18.0%)
- Phenytoin	0 (0.0%)	5 (16.7%)	2 (10.5%)	0 (0.0%)	1 (20.0%)	8 (13.1%)
- Carbamazepine	0 (0.0%)	0 (0.0%)	3 (15.8%)	0 (0.0%)	0 (0.0%)	3 (4.9%)
- Oxcarbazepine	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
Chemotherapy	2 (40.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (4.9%)
NSAIDs	1 (20.0%)	0 (0.0%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	3 (4.9%)
Others	0 (0.0%)	1[a] (3.3%)	1[b] (5.3%)	0 (0.0%	1[c] (20.0%)	3 (4.9%)
Infection						
HSV	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
S. pneumoniae	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
Idiopathic	0 (0.0%)	0 (0.0%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	2 (3.3%)
Latency period (days)	1.7 ± 1.2	13.9 ± 8.0	13.3 ± 11.2	14.5 ± 3.5	22.2 ± 22.4	15.3 ± 14.3

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; SJS/TEN overlap, Stevens-Johnson syndrome/toxic epidermal necrolysis overlap; TEN, toxic epidermal necrolysis; NSAIDs, non-steroidal anti-inflammatory drugs; HSV, herpes simplex virus; *S. pneumoniae*, *Streptococcus pneumoniae*

†There were 61 possible causes of SCARs identified from 52 cases in this study.

[a]deferasirox; [b]sulfasalazine; [c]lidocaine

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Table 3. Clinical characteristics and laboratory investigations of the 52 included SCARs patients.

	AGEP (n = 3)	DRESS (n = 23)	SJS (n = 19)	SJS/TEN overlap (n = 2)	TEN (n = 5)	Total (N = 52)	*p*-value
Fever	1 (33.3%)	17 (73.9%)	10 (52.6%)	0 (0.0%)	4 (80.0%)	32 (61.5%)	0.099
Tachycardia	2 (66.7%)	17 (73.9%)	12 (63.2%)	1 (50.0%)	4 (80.0%)	36 (69.2%)	0.848
Tachypnea	3 (100%)	11 (47.8%)	8 (42.1%)	1 (50.0%)	4 (80.0%)	27 (51.9%)	0.137
Edema	0 (0.0%)	1 (4.3%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	2 (3.8%)	0.100
Abnormal breath sounds	0 (0.0%)	4 (17.4%)	2 (10.5%)	0 (0.0%)	1 (20.0%)	7 (13.5%)	0.875
Hepatomegaly	0 (0.0%)	11 (47.8%)	1 (5.3%)	0 (0.0%)	1 (20.0%)	13 (25.0%)	0.014
Splenomegaly	0 (0.0%)	4 (17.4%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	5 (9.6%)	0.244
Lymphadenopathy	0 (0.0%)	9 (39.1%)	1 (5.3%)	0 (0.0%)	1 (20.0%)	11 (21.2%)	0.073
Hypotension	1 (33.3%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	3 (5.8%)	0.106
Rash							
- Maculopapular	3 (100%)	21 (91.3%)	14 (73.7%)	0 (0.0%)	5 (100%)	43 (82.7%)	**0.023**
- Target lesions	0 (0.0%)	0 (0.0%)	12 (63.2%)	2 (100%)	3 (60.0%)	17 (32.7%)	**< 0.001**
- Vesicobullous lesions	0 (0.0%)	0 (0.0%)	8 (42.1%)	2 (100%)	4 (80.0%)	14(26.9%)	**< 0.001**
- Erosions	0 (0.0%)	2 (8.7%)	3 (15.8%)	0 (0.0%)	0 (0.0%)	5 (9.6%)	0.445
- Purpura	0 (0.0%)	1 (4.3%)	4 (21.1%)	0 (0.0%)	0 (0.0%)	5 (9.6%)	**< 0.001**
- Desquamation	0 (0.0%)	3 (13.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	4 (7.7%)	0.840
- Pustules	3 (100%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	4 (7.7%)	0.226
- Erythema	0 (0.0%)	2 (8.7%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	3 (5.8%)	0.670
- Skin necrosis	0 (0.0%)	0 (0.0%)	2 (10.5%)	0 (0.0%)	1 (20.0%)	3 (5.8%)	0.366
- Exfoliative dermatitis	0 (0.0%)	2 (8.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.8%)	0.883
- Nikolsky's sign	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)	2 (3.8%)	**0.023**
- Tenderness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)	2 (3.8%)	**0.023**
Mucosal involvement	0 (0.0%)	6 (26.1%)	17 (89.5%)	2 (100%)	4 (80.0%)	29 (55.8%)	**< 0.001**
- Ocular	0 (0.0%)	5 (21.7%)	14 (73.7%)	2 (100%)	4 (80.0%)	25 (48.1%)	**< 0.001**
- Oral	0 (0.0%)	4 (17.4%)	14 (73.7%)	2 (100%)	4 (80.0%)	24 (46.2%)	**< 0.001**
- Anal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (1.9%)	0.192
- Genitourinary	0 (0.0%)	1 (4.3%)	9 (47.4%)	1 (50.0%)	4 (80.0%)	15 (28.8%)	**< 0.001**

Table 3. (Continued)

	AGEP (n = 3)	DRESS (n = 23)	SJS (n = 19)	SJS/TEN overlap (n = 2)	TEN (n = 5)	Total (N = 52)	*p*-value
Hematologic	3 (100%)	21 (91.3%)	14 (73.7%)	2 (100%)	4 (80.0%)	44 (84.6%)	0.636
- Anemia	3 (100%)	12 (52.2%)	6 (31.6%)	1 (50.0%)	4 (80.0%)	26 (50.0%)	1.000
- Leukocytosis	2 (66.7%)	9 (39.1%)	5 (26.3%)	1 (50.0%)	1 (20.0%)	18 (34.6%)	0.604
- Neutrophilia	2 (66.7%)	6 (26.1%)	6 (31.6%)	1 (50.0%)	2 (40.0%)	17 (32.7%)	0.664
- Eosinophilia	2 (66.7%)	11 (47.8%)*	4 (21.1%)	0 (0.0%)	0 (0.0%)	17 (32.7%)	0.079
- Lymphopenia	1 (33.3%)	3 (13.0%)	4 (21.1%)	1 (50.0%)	1 (20.0%)	10 (19.2%)	0.472
- Thrombocytopenia	0 (0.0%)	7 (30.4%)	3 (15.8%)	0 (0.0%)	0 (0.0%)	10 (19.2%)	0.554
- Leukopenia	1 (33.3%)	5 (21.7%)	2 (10.5%)	0 (0.0%)	1 (20.0%)	9 (17.3%)	0.733
- Presence of atypical lymphocytes	0 (0.0%)	2 (8.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.639
Inflammatory markers	0 (0.0%)	6 (26.1%)	3 (15.8%)	0 (0.0%)	2 (40.0%)	11 (21.1%)	0.573
- Elevated ESR	0 (0.0%)	4 (17.4%)	2 (10.5%)	0 (0.0%)	2 (40.0%)	8 (15.4%)	0.503
- Elevated CRP	0 (0.0%)	4 (17.4%)	2 (10.5%)	0 (0.0%)	1 (20.0%)	7 (13.5%)	0.875
Urinary	0 (0.0%)	3 (13.0%)	5 (26.3%)	1 (50.0%)	2 (40.0%)	12 (23.1%)	0.733
- Proteinuria	0 (0.0%)	3 (13.0%)	4 (21.1%)	0 (0.0%)	2 (40.0%)	9 (17.3%)	0.844
- Hematuria	0 (0.0%)	0 (0.0%)	3 (15.8%)	1 (50.0%)	0 (0.0%)	4 (7.7%)	0.330
- Pyuria	0 (0.0%)	0 (0.0%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	2 (3.8%)	0.707
Liver	1 (33.3%)	21 (91.3%)	8 (42.1%)	1 (50.0%)	3 (60.0%)	34 (65.4%)	**0.004**
- Elevated AST	0 (0.0%)	20 (87.0%)	5 (26.3%)	1 (50.0%)	2 (40.0%)	28 (53.8%)	**<0.001**
- Elevated ALT	0 (0.0%)	18 (78.3%)	6 (31.6%)	1 (50.0%)	1 (20.0%)	26 (50.0%)	**0.004**
- Elevated direct bilirubin	0 (0.0%)	9 (39.1%)	4 (21.1%)	0 (0.0%)	3 (60.0%)	16 (30.8%)	0.411
- Low albumin	1 (33.3%)	8 (34.8%)	3 (15.8%)	0 (0.0%)	2 (40.0%)	14 (26.9%)	0.684
- Elevated total bilirubin	0 (0.0%)	6 (26.1%)	1 (5.3%)	0 (0.0%)	1 (20.0%)	8 (15.4%)	0.429
Renal and electrolytes	2 (66.7%)	13 (56.5%)	10 (52.6%)	1 (50.0%)	3 (60.0%)	29 (55.8%)	0.955
- Metabolic acidosis	0 (0.0%)	7 (30.4%)	5 (26.3%)	1 (50.0%)	3 (60.0%)	16 (30.8%)	0.886
- Hypokalemia	2 (66.7%)	6 (26.1%)	5 (26.3%)	0 (0.0%)	1 (20.0%)	14 (26.9%)	0.394
- Hyponatremia	0 (0.0%)	7 (30.4%)	2 (10.5%)	0 (0.0%)	2 (40.0%)	11 (21.2%)	0.394
- Hypochloremia	0 (0.0%)	4 (17.4%)	1 (5.3%)	0 (0.0%)	2 (40.0%)	7 (13.5%)	0.415
- Elevated BUN	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	2 (3.8%)	0.501
- Elevated creatinine	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	2 (3.8%)	0.351

A *p*-value < 0.05 indicates statistical significance.

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; SJS/TEN overlap, Stevens-Johnson syndrome/toxic epidermal necrolysis overlap; TEN, toxic epidermal necrolysis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen

Table 4. Treatment and outcome of the 52 included SCARs patients.

	AGEP (n = 3)	DRESS (n = 23)	SJS (n = 19)	SJS/TEN overlap (n = 2)	TEN (n = 5)	Total (N = 52)
Treatment						
Drug withdrawal	1 (33.3%)	23 (100.0%)	13 (68.4%)	1 (50.0%)	5 (100.0%)	43 (82.7%)
Eye consultation	1 (33.3%)	7 (30.4%)	16 (84.2%)	2 (100.0%)	5 (100.0%)	31 (59.6%)
Analgesics	2 (66.7%)	14 (60.9%)	12 (63.2%)	1 (50.0%)	5 (100.0%)	34 (65.4%)
Systemic corticosteroids	0 (0.0%)	15 (65.2%)	10 (52.6%)	2 (100.0%)	4 (80.0%)	31 (59.6%)
Oral prednisolone	0 (0.0%)	14 (60.9%)	9 (47.4%)	1 (50.0%)	2 (40.0%)	26 (50%)
IV methyprednisolone	0 (0.0%)	3 (13%)	3 (15.8%)	1 (50.0%)	1 (20.0%)	8 (15.4%)
IV hydrocortisone	0 (0.0%)	2 (8.7%)	1 (5.3%)	0 (0.0%)	3 (60.0%)	6 (11.5%)
IV dexamethasone	0 (0.0%)	0 (0.0%)	3 (15.8%)	0 (0.0%)	2 (40.0%)	5 (9.6%)
IVIg	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (60.0%)	3 (5.8%)
NAC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (1.9%)
Antibiotics	1 (33.3%)	9 (39.1%)	10 (52.6%)	0 (0.0%)	5 (100.0%)	25 (48.1%)
Ocular management	1 (33.3%)	3 (13.0%)	16 (84.2%)	2 (100.0%)	5 (100.0%)	27 (51.9%)
Eye irrigation	0 (0.0%)	0 (0.0%)	3 (15.8%)	0 (0.0%)	2 (40.0%)	5 (9.6%)
Artificial tears	1 (33.3%)	7 (30.4%)	16 (84.2%)	2 (100.0%)	5 (100.0%)	31 (59.6%)
Ocular antibiotics	0 (0.0%)	2 (8.7%)	11 (57.9%)	2 (100.0%)	4 (80.0%)	19 (36.5%)
Ocular steroids	1 (33.3%)	3 (13.0%)	10 (52.6%)	2 (100.0%)	4 (80.0%)	20 (38.5%)
Outcomes						
Discharge status						
Fully recovery	0 (0.0%)	4 (17.4%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	5 (9.6%)
Improved	3 (100%)	19 (82.6%)	18 (94.7%)	2 (100.0%)	4 (80.0%)	46 (88.5%)
Dead	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (1.9%)
Cases to follow up (cases)	2 (66.7%)	15 (65.2%)	12 (63.2%)	2 (100.0%)	2 (40.0%)	33 (63.5%)
Mean follow up duration (months)	1	5.6	29.8	36	1.5	15.7
Acute complications						
Superimposed skin infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (1.9%)
Ocular	0 (0.0%)	1 (4.3%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	3 (5.8%)
Long-term outcome						
Fully recovery	2 (66.7%)	11 (47.8%)	5 (26.3%)	0 (0.0%)	0 (0.0%)	18 (34.6%)
Recovery with complications	0 (0.0%)	4 (17.4%)	7 (36.8%)	2 (100.0%)	2 (40.0%)	15 (28.8%)
Recurrent SCARs	1 (33.3%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.8%)
Loss to follow up/dead	1 (33.3%)	7 (30.4%)	7 (36.8%)	0 (0.0%)	3 (60.0%)	18 (34.6%)
Long-term complications						
Dermatologic	0 (0.0%)	5 (21.7%)	4 (21.1%)	2 (100.0%)	0 (0.0%)	11 (21.2%)
Ocular	0 (0.0%)	1 (4.3%)	5 (26.3%)	1 (50.0%)	2 (40.0%)	9 (17.3%)
Endocrine†	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; IVIg, intravenous immunoglobulin; NAC, N-acetylcysteine; PIH, post-inflammatory hyperpigmentation; SCARs, severe cutaneous adverse drug reactions; SJS, Stevens-Johnson syndrome; SJS/TEN overlap, Stevens-Johnson syndrome/toxic epidermal necrolysis overlap; TEN, toxic epidermal necrolysis
†Non-thyroidal illness

Each SCARs type had its own characteristic rashes. All cases with AGEP had pustular and maculopapular eruption. AGEP was found to be statistically correlated with pustules ($p < 0.001$). DRESS patients had multiple morphology of rash, with maculopapular rash (73.9%) being the most prevalent. Target lesions ($p < 0.001$), vesicobullous lesions ($p < 0.001$), purpura ($p < 0.001$), positive Nikolsky's sign ($p = 0.023$), and skin tenderness ($p = 0.023$) were found to commonly occur in blistering SCARs.

Ocular (n = 25, 48.1%), oral (n = 24, 46.2%), and genitourinary (n = 15, 28.8%) mucosal involvement were significantly presented in SJS/TEN ($p < 0.001$). Genitourinary lesions ($p = 0.021$) were significantly found in 80% of TEN patients. Most patients with mucosal lesions (n = 22, 78.8%) had at least two sites of involvement.

Laboratory investigations are also shown in **Table 3**. Anemia (82.7%) was the most common hematologic finding. White blood cell abnormalities included leukocytosis (34.6%), eosinophilia (32.7%), lymphopenia (19.2%), and leukopenia (17.3%). Eosinophilia was common in both AGEP (66.7%) and DRESS (47.8%); however, only DRESS was shown to be statistically related with eosinophilia when compared between DRESS and the others ($p = 0.047$). Seven DRESS patients (30.4%) and three SJS patients (15.8%) had thrombocytopenia. Coagulopathy was quite uncommon. Inflammatory markers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were elevated in approximately 21.1% of cases, and most of those cases were diagnosed with DRESS. Urinary abnormalities, including mild proteinuria (17.3%), hematuria (7.7%), and pyuria (3.8%), were found mainly in those diagnosed with SJS. However, renal function often remained unaffected. Liver was the only major organ involvement found to be significantly correlated with DRESS ($p = 0.004$), compared to other SCARs types. Elevated aspartate transaminase (AST) and alanine transaminase (ALT) were reported with a prevalence of 87% and 78.3%, respectively. Electrolyte abnormalities, including metabolic acidosis (30.8%) and hypokalemia (26.9%) were reported.

Human leukocyte antigen (HLA) *B*1502* screening was performed to identify patients at high risk for carbamazepine hypersensitivity. Only 3 of cases were tested, and there were 2 positive results. One patient with SJS caused by carbamazepine was found to be positive for *HLA-B*1502* after the diagnosis of SJS was made.

The mainstay of treatment for SCARs caused by medication (89.6%) was drug discontinuation. The need for such treatment, such as meropenem in severe sepsis, was noted as the reason for continuing the culprit drug(s) despite the onset of SCARs. Antibiotics were prescribed in 25 patients (48.1%). The most common reason was the need to treat a concurrent serious infection. Analgesics (65.4%) and antihistamines (78.85%) were given to comfort patients. The most commonly prescribed ophthalmic preparations were artificial tears and a combination of topical antibiotics and corticosteroids. Systemic corticosteroids were administered in 65.2% of DRESS, 52.6% of SJS (n = 10), 100% of SJS/TEN overlap, and 100% of TEN, with doses ranging from 0.5-2 mg/kg/day of prednisolone-equivalent dose. A significantly shorter median length of hospital stay was observed in DRESS ($p = 0.014$, 95%CI -10.712 to 93.312) and blistering SCARs patients ($p = 0.012$, 95%CI -7.49 to 61.75) who received the medication. The only significant correlation found that faster initiation of systemic corticosteroids (1.83 ± 3.53 days) was related to a shorter length of stay in DRESS ($r = 0.734$, $p < 0.001$). There was no correlation found between the duration of systemic corticosteroids and the length of stay in all groups. Intravenous immunoglobulin (IVIg) (60%) and intravenous N-acetylcysteine (20%) were prescribed only in patients diagnosed with TEN. IVIg doses ranged from a total of 1-4 g/kg/course over 1-4 days. Moderate-potency topical corticosteroids were prescribed in 32.7% of overall SCARs cases. Nutritional and hydration support, along with electrolytes correction were all essential for patient management. Other supportive treatments that were given included bland moisturizers and wet dressing of erosive lesions.

Most of the cases (88.5%) had improved dramatically at discharge. The average follow-up duration was 15.7 months, and the longest follow-up duration was in the SJS/TEN group. One patient diagnosed with DRESS (4.3%) had a disease relapse at week 4 of prednisolone tapering, presenting with a newly-erupted maculopapular rash and transaminitis. The dose of the medication needed to be increased for a short period and was weaned off later without complication. One patient with TEN died, giving an overall mortality rate of 1.9%, and a TEN mortality rate of 20%. The cause of death was septic shock and disseminated intravascular coagulation (DIC). That patient had fever and diarrhea for 9 days, and rash for 5 days prior to hospital admission. TEN was diagnosed at first and therapy was provided. Delayed hospital visit was likely contributed to the fatal outcome in that case.

Acute complications that developed within 1 month after the diagnosis of SCARs mostly involved the ocular (5.8%) or dermatologic (3.8%) systems. Eighteen patients (35.3%) were lost to follow-up. The follow-up duration was significantly longer in cases with acute ($p < 0.001$) and long-term ($p < 0.001$) ocular complications compared to those who did not have such complications. Keratitis and corneal scars were commonly found in 26.3% of SJS cases. Regarding the final outcome, 34.6% of patients fully recovered, and another 28.8% had long-term complications. The only treatment complication reported was ocular hypertension due to prolonged use of ophthalmic corticosteroids.

Discussion

Incidence of SCARs in children does not differ from that observed in adults. They affect people of both genders nearly equally with slight female predominance.[2,4,5] In this study, DRESS was the most commonly observed SCARs, in contrast to previous studies that reported SJS to be the most common type.[1,4] Underlying diseases, especially epilepsy, malignancy, and infection are prevalent in patients with SCARs.

The main culprit drugs in our study were anticonvulsants and antimicrobial agents, consistent with previous reports in children[6-8] and adults.[1,9-11] In AGEP, a different pattern of etiology was proposed, with antibiotics having the strongest link to the condition, and antiepileptic medications having a less convincing association.[11] Our data concerning latency period, which was defined as the duration from medication administration to the onset of adverse reaction, differs from the report by Mustafa, et al. who found that AGEP had the shortest latency period, and DRESS had the longest latency period.[10] We found that TEN had the longest latency period, and that AGEP had the shortest. This inconsistency may be another important issue to explore since this knowledge is useful for determining the causality of SCARs and the suspected medications. The limited sample size of this study might be one of the attributable factors.

AGEP

AGEP is a rare form of SCARs in children that has a comparatively lower level of severity compared to the other types of pediatric SCARs.[10] AGEP has been linked to several causes, including medications and infections. Previous study proposed infectious etiology to be more common in pediatric AGEP compared to adults.[7] However, since we only had 3 cases with AGEP, it was difficult to discern a pattern of causation. The clinical presentation in our cases was similar to that observed in another study population in which maculopapular rash preceded subcorneal pustular eruptions in most patients.[12] Leukocytosis, neutrophilia, and eosinophilia were found in 66.7% of our AGEP patients. Prevalence of eosinophilia was inconsistent in previous studies, ranging from 8-83%. Mechanism of AGEP has not yet been clearly understood, some particular interleukines (IL) may play a role and lead to neutrophilia (IL-3 and IL-8) and eosinophilia (IL-5).[12,13] We believe that further research needs to be done on this matter. Mucosal involvement is rarely found in AGEP, and none of our cases experienced this manifestation. AGEP was reported to be self-limiting over a short duration course that ranged from 4-15 days.[7,12] Topical corticosteroids hastened the resolution of lesions in 1 patient. All AGEP patients had a favorable outcome.

DRESS

Among 23 DRESS cases in our study, the median age at diagnosis was 94 months. The average latency period was 13.9 days, shorter than that reported from previous studies.[5,14] The main culprit agents were antibiotics and antiepileptic drugs. The median length of hospital stay was 25 days, significantly longer in cases with acute complications ($p < 0.001$, 95%CI 3.06-98.73). Consistent with other studies,[9,15] classical presentations, including fever, tachycardia, hepatomegaly, lymphadenopathy, and maculopapular rash, were common. Ocular and/or oral involvement was found in 12-20% of cases, which is similar to the reported findings of Afiouni, et al.[5]

Eosinophilia is one of the most frequent hematologic findings in DRESS.[16] Despite it being one of the parameters in the RegiSCAR criteria, the extent of the prevalence of thrombocytopenia in DRESS remains controversial. Some studies[5,17] reported thrombocytopenia to be uncommon, while a different study reported that it occurs frequently.[18] In our study, the number of DRESS with thrombocytopenia was high at 30.4%. However, various medical conditions could also affect number of platelet count and result in this discrepancy.

Elevated AST and/or ALT were observed in 73-94.2% of DRESS. Electrolytes imbalances were also common.[5,9] Balachandra, et al.[19] reported that 62% of patients with fever, exanthem, hepatomegaly, lymphadenopathy, and leukocytosis, mimicking the clinical picture of DRESS, were seropositive for HHV-6. This highlights the need for future research in this potential relationship.

There is no standard guideline for the management of pediatric DRESS. Elimination of the culprit is still the most important measure. Systemic corticosteroids are one of the most common therapies in DRESS. In our study, corticosteroids were administered to two-thirds of DRESS patients with varying doses and durations depending on clinical severity. Concurrent infection and mild disease severity were the major reasons for not prescribing systemic corticosteroids for the rest. As mentioned above, systemic corticosteroids resulted in a shorter length of hospital stay. The earlier the corticosteroids were administered, the shorter the length of stay tended to be. However, the duration of systemic corticosteroids had no impact on the length of stay. Acute and long-term complication rates were shown to be unaffected by systemic corticosteroids. No patient needed to withdraw from systemic corticosteroids treatment. Many studies also advocated the use of systemic corticosteroids in pediatric DRESS.[5,6] Nearly 65% of our DRESS cases recovered completely. Disease relapse occurred in 4.3%, which was low compared to other reports.[20,21] There were no death among DRESS patients in this study. The lesser severity of DRESS and the underlying disorders in most of our patients may have contributed to fewer deaths. Previous studies in pediatric DRESS reported a mortality rate of approximately 3%.[5,6] The mentioned causes of death were fulminant hepatitis, coagulopathy, and sepsis.[6]

SJS, TEN, SJS/TEN overlap

SJS, TEN, and SJS/TEN overlap are clinical spectrum disorders with similar pathogenesis and histologic features.[22] The median age at diagnosis in our SJS/TEN group patients was 99 months. The latency period among these 3 conditions ranged from 13.3-22.2 days. The length of hospital stay was longest in TEN. Drugs were the culprit in 72-90% of SJS/TEN cases.[23] Antiepileptic and antimicrobial drugs were the leading culprits, which is consistent with the findings of other studies.[1,10,23] Infectious etiology, including herpes simplex virus (HSV) and *Streptococcus pneumoniae* (*S. pneumoniae*), might be a trigger,[24] as found in two of our SJS cases. Fever, tachycardia, and tachypnea were common clinical signs. The dermatologic manifestations of SJS, SJS/TEN overlap, and TEN are similar. Maculopapular eruptions preceding target lesions and positive Nikolsky's sign are the main findings. Vesicobullous lesions and purpura were also reported to be highly prevalent.[25] Mucosal involvement is a key hallmark of these disorders with a rate of 100% in the study by Sato, et al.[26] and 88.5% in ours. Ocular and oral mucosa were the two most common sites of injury.

Laboratory findings are usually nonspecific and have little diagnostic value in SJS/TEN. Hematologic abnormalities, such as anemia and leukocytosis, can be found. Hepatic and renal injury might result from the culprit drugs, the conditions themselves, or from other comorbidities. Likewise, these laboratory tests should be done in SJS/TEN patients.

Previous studies suggested the risk of infection, complications, and mortality to be higher in SJS/TEN patients who received systemic corticosteroids,[27] or concluded that systemic corticosteroid treatment had no beneficial effect on disease outcome.[28] In contrast, later evidence suggested that systemic corticosteroids did not increase risk of infection, and could even reduce mortality risk when combined with IVIg.[29,30] Systemic corticosteroids were used in half of our SJS patients, and in nearly all of our SJS/TEN overlap and TEN cases. Shorter hospital stays were associated with systemic corticosteroids, but there was no change in the rate of acute and long-term complications. The duration of the medication or the time it was given had no impact on the length of stay. Treatment of mucosal involvement must be individualized because the severity and scope of involvement differs from patient to patient. Ocular complications require proper ophthalmologic treatment from the time of diagnosis. Since SJS patients generally have a more severe mucosal involvement, ocular complications, such as symblepharon, corneal scarring, and dry eyes, will be more commonly found.

TEN mortality rate was 20% in our study, comparable to the previously reported rates of 20-35%.[22] In contrast, other studies reported a much lower mortality rate among pediatric TEN patients ranging from 6.6-15.1%.[8,31]

In vitro testing of delayed type hypersensitivity reactions was not performed in the majority of our cases due to the high cost and the limited availability of tests, especially during the early years of the study period. The same trend was observed concerning tests to identify cases at higher risk for drug hypersensitivity, such as HLA testing for anticonvulsants. Some of these tests are now more accessible. We would like to highlight the importance of performing tests to identify high-risk patients for specific drugs, as well as for determining the definite etiology of SCARs.

Limitations

This study has some mentionable limitations. First, the retrospective design may result in missing or incomplete data, certain biases, the inability to prove absolute causality. Second, our data was collected from a single national tertiary referral. Some of our data may not be generalizable to other levels of care. Third, the size of our study population was relatively small due to the rarity of SCARs in children. This may limit the statistical power of our study to identify all statistically significant differences and associations between and among groups. Further multicenter study in a larger study population should be considered.

Conclusion

SCARs in pediatric patients cause significant morbidity and mortality similar to that observed in adults. Our results showed anticonvulsants and antimicrobials to be leading causes of SCARs. Clinical manifestations, including fever, hallmark skin rashes, and mucosal involvement, can lead to timely and accurate diagnosis and proper management. Laboratory investigations aid in diagnosing DRESS and highlight high-risk SCARS cases. Treatment of SCARs varies according to clinical presentation and severity of the reaction.

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Conflict of Interest

All authors declare no personal or professional conflicts of interest relating to any aspect of this study.

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Author Contributions

- **Author 1:** Methodology, validation, formal analysis (lead), writing - original draft, and visualization (lead);
- **Author 2:** Conceptualization, methodology(lead), validation, formal analysis, and writing – review & editing;
- **Author 3:** Conceptualization (lead), methodology, validation, formal analysis, writing – review & editing (lead), visualization, and corresponding author.
- All authors approved the final manuscript.

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