Original Article

Severe Cutaneous Adverse Drug Reactions in Pediatric Patients: A Multicenter Study

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What is already known about this topic? Severe cutaneous adverse drug reactions (SCARs) are rare in children, but potentially may cause morbidity and mortality, and therefore should be treated promptly and appropriately.

What does this article add to our knowledge? Data on pediatric patients with SCARs are limited, and our study suggests that the most common causative agents are drugs, especially antibiotics in children.

How does this study impact current management guidelines? A high index of suspicion should be maintained to make a rapid diagnosis and manage SCARs in children. There is no consensus yet on the topic of effective systemic and topical treatment of SCARs. Further studies are needed to establish standardized management protocols.

BACKGROUND: The severe cutaneous adverse drug reactions (SCARs) are rare but could be life-threatening. These include drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis.
OBJECTIVE: The purpose of this study was the evaluation of the clinical characteristics of patients with the diagnosis of SCARs.
METHODS: Patients who were diagnosed with SCARs between January 2011 and May 2016 by pediatric allergy clinics in the provinces of Ankara, Trabzon, Izmir, Adana, and Bolu were included in this multicenter study. Clinical and laboratory findings, the time between suspected drug intake and development of clinical findings, treatments they have received, and length of recovery time were recorded.
RESULTS: Fifty-eight patients with SCARs were included in this study. The median age of the patients was 8.2 years (interquartile range, 5.25-13 years) and 50% (n = 29) were males. Diagnosis was Stevens-Johnson syndrome/TEN in 60.4% (n = 35), DRESS in 27.6% (n = 16), and acute generalized exanthematous pustulosis in 12% (n = 7) of the patients. In 93.1% of the patients, drugs were the cause of the reactions. Antibiotics ranked first among the drugs (51.7%) and antiepileptic drugs were the second (31%) most common. A patient who was diagnosed with TEN developed lagophthalmos and a patient who was diagnosed with DRESS developed secondary diabetes mellitus. Only 1 patient with the diagnosis of TEN died.
CONCLUSIONS: SCARs in children are not common but potentially serious. Early diagnosis and appropriate treatment of SCARs will reduce the incidence of morbidity and mortality. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Acute generalized exanthematous pustulosis; Children; DRESS; Eosinophilia; Stevens-Johnson syndrome; Severe cutaneous adverse drug reactions; Toxic epidermal necrolysis*

In the pediatric population, cutaneous reactions constitute 35% to 36% of adverse drug reactions.[1] Despite the high prevalence of cutaneous adverse drug reactions, they are mostly of benign character and cause mild clinical symptoms and subside spontaneously with discontinuation of the suspected drug.[2] However, 2% to 6.7% of cutaneous reactions can develop into severe and potentially life-threatening clinical syndromes.[3,4] The early recognition of these clinical conditions and discontinuation of the suspected drug is important.

Acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)

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Abbreviations used
AGEP- Acute generalized exanthematous pustulosis
DRESS- Drug rash with eosinophilia and systemic symptoms
IVIG- Intravenous immunoglobulin
RegiSCAR- Registry of Severe Cutaneous Adverse Reactions
SCARs- Severe cutaneous adverse drug reactions
SCORTEN- A severity of illness score specified for TEN
SJS- Stevens-Johnson syndrome
TEN- Toxic epidermal necrolysis

syndrome, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) are among the severe cutaneous adverse drug reactions (SCARs).[2] Although pathogenesis is not completely understood, SCARs are thought to occur because of T-cell–mediated delayed immune mechanisms.[4]

Drug exposure is the most common cause of severe cutaneous reactions, and most common drugs reported to be associated with SCARs are antiepileptic drugs, antimicrobials, allopurinol, and nonsteroidal inflammatory drugs.[3]

Considering serious morbidity along with mortality, early diagnosis and treatment is crucial. The mortality rates are 10% for DRESS,[5] 1% to 5% for SJS, 25% to 35% for TEN,[6] and less than 5% for AGEP.[7] Suspicion based on clinical history is essential, whereas a skin biopsy may confirm the diagnosis. Patch test may be useful to determine the susceptible agent.[8] Provocation test is contraindicated in these patients.[8]

SCARs are rarely seen in children,[1] and data on the characteristics of SCARs in this age group are limited. In this multicenter study, we analyzed the clinical characteristics, laboratory findings, treatment, and prognosis of children who developed SCARs.

METHODS

Study population

Patients who were diagnosed with SCARs between January 2011 and May 2016 by pediatric allergy clinics in the provinces of Ankara, Trabzon, Izmir, Adana, and Bolu (Ankara Children's Hematology Oncology Training and Research Hospital, Izmir Dr. Behcet Uz Children's Hospital, Training and Research Hospital, Karadeniz Technical University Faculty of Medicine, Adana Obstetrics and Pediatrics Hospital, and Bolu Abant Izzet Baysal University Faculty of Medicine) were included in this multicenter study. The age and sex of the patients, suspected drug/drugs, the time interval between drug intake and the development of clinical signs, comorbidities, history of drug reactions, physical examination and laboratory findings, the treatment they received and its duration, length of stay in the hospital, diagnostic tests, and the state of morbidity and mortality were recorded.

The study was approved by the ethical committee of Ankara Children's Hematology Oncology Training and Research Hospital.

DRESS syndrome

In patients with a history of drug use, the possibility of DRESS syndrome was evaluated using the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system on the basis of the presence of mucocutaneous rash, fever, lymphadenopathy, and hematological anomalies such as eosinophilia, atypical lymphocytes, and internal organ involvement. Using RegiSCAR, those with a score of under 2 points were diagnosed as "not DRESS," those with a score of 2 to 3 points were diagnosed as "possible DRESS," those with a score of 4 to 5 points as suffering from "probable DRESS," and those with a score of more than 5 points were diagnosed as suffering from "DRESS."[9]

SJS/TEN

Although there are no universally accepted criteria, diagnosis is based on cutaneous and mucous membrane manifestations, systemic involvement, and histological findings. Acute onset of mucous membrane involvement (at least 2 mucosal surfaces) and skin symptoms (maculae, target-like, bullae or erosion, positive Nikolsky sign) together with epidermal detachment of less than 10% of the total body surface area are regarded as SJS. Epidermal detachment of more than 30% of the total body surface area together with similar clinical signs is classified as TEN and 10% to 30% epidermal detachment as SJS/TEN overlap.[10]

The SCORTEN (a severity of illness score specified for TEN) scoring system was used as a standard prognostic tool in the prediction of mortality for TEN. This system is based on 7 clinical and laboratory variables, with 1 point given in the presence of each of the following criteria: age 40 years or more, presence of a concomitant malignancy, pulse 120/min or more, blood urea nitrogen more than 28 mg/dL, serum glucose 252 mg/dL, serum bicarbonate less than 20 mmol/L, and involved body surface area more than 10% and 0 point was given in the absence of these parameters.[11]

AGEP

AGEP was considered in the presence of nonfollicular, pustular lesions less than 5 mm that form on the erythematous skin occurring within a few days following the first dose of the drug. The European Study of Severe Cutaneous Adverse Reactions scoring system was used for diagnosis. According to this score; less than 0 points is labeled as not AGEP, 1 to 4 points as possible AGEP, 5 to 7 points as probable AGEP, and 8 to 12 points as definite AGEP.[12]

Diagnostic tests

Skin biopsies and patch testing were performed for patients when an informed consent could be obtained. The skin biopsy was performed before treatment from the lesion area as a punch biopsy.

Patch test was carried out at least 6 weeks after the resolution of symptoms. In accordance with the European Network for Drug Allergy guidelines, the patch test was prepared homogeneously with petrolatum (solid Vaseline) with suggested concentration and each drug was placed in an aluminum chamber (Finn Chambers) and adhered on the patient's back.[13] Petrolatum was used as a negative control. Two readings were carried for each patient. The first was after removal of the patch test on second day and the second was to reevaluate on the 72nd hour.[14]

Evaluation of the etiology

To identify culprit drugs, the patients were evaluated in terms of the medication history, latency period between drug introduction and symptoms, and clinical course after discontinuation of the suspected drug. When parents have given consent, patch test with the suspected drug was performed. To detect the responsible infectious agent in the patients who had symptoms of any recent infection, serologic tests including EBV, cytomegalovirus, herpes simplex virus type 1 and 2, varicella zoster virus, parvovirus, rubella, rubeola, hepatitis A, hepatitis B, and mycoplasma pneumonia were performed. If the patients had both infectious symptoms and positive serologic test results, the etiology was attributed to the infection.

TABLE I. Etiology of patients

Etiology	SJS/TEN (n = 35)	DRESS (n = 16)	AGEP (n = 7)
Drugs	31 (88.6)	16 (100)	7 (100)
Antibiotics	16 (45.7)	8 (50)	6 (85.7)
Amoxicillin-clavulanate	3	3	2
Ampicillin sulbactam	5	1	1
Ceftriaxone	1	—	2
Cefuroxime	1	—	—
Cefazolin	1	—	—
Cefixime	1	—	—
Cefdinir	1	2	—
Cefotaxime	-	1	—
Clarithromycin	2	1	1
Multiple antibiotics (vankomycin, cotrimoxazole, amphotericin B)	1	—	—
Antiepileptics	12 (34.3)	6 (37.5)	—
Carbamazepine	6	3	—
Lamotrigine	3	1	—
Phenytoin	1	1	—
Phenobarbital	1	1	—
Clobazam	1	—	—
Multiple drugs	2 (5.7)	—	—
Clindamycin, meropenem, amikacin, prednisolone	1	—	—
Lansoprazole, prednisolone	1	—	—
Nonsteroidal anti-inflammatory drugs	1 (4.3)	—	—
Metamizole	1	—	—
Other drugs	—	2 (12.5)	1 (14.3)
Ifosfamide + doxorubicin	—	—	1
Sulfasalazine	—	1	—
Oxymetazoline nasal spray	—	1	—
Infectious agents	3 (8.6)	—	—
Mycoplasma	2	—	—
Herpes simplex virus type 1	1	—	—
Unknown	1 (4.3)	—	—

Values are n (%).

Statistical analysis

Statistical analyses were performed using the SPSS 22.0 statistical software package (SPSS, Inc, Chicago, Ill) for Windows. The definitions were provided as number and percentage for discrete variables and mean and SD for continuous variables.

RESULTS

Fifty-eight patients with SCARs were evaluated in this study. The median age of the patients was 8.2 years (interquartile range [IQR], 5.25-13 years) and 50% (n = 29) were males. The diagnosis was SJS/TEN in 60.4% (n = 35) of the patients, DRESS in 27.6% (n = 16), and AGEP in 12% (n = 7).

In 93.1% of the patients, drugs were the cause of the reactions. Antibiotics ranked first among the drugs (51.7%) and antiepileptic drugs were second most common (31%). Although infectious factors played a role in the etiology of 3 (5.2%) patients, the etiology of 1 (1.7%) patient could not be determined (Table I).

Patients with SJS/TEN

In the SJS/TEN group, 80% (n = 28) of the patients had SJS, 11.4% (n = 4) had TEN, and 8.6% (n = 3) had SJS/TEN overlap. Drugs played a role in the etiology in 88.6% (31 of 35) of the patients, including antibiotics (45.7%) and antiepileptic drugs (34.3%). For all the patients who were diagnosed as suffering from TEN, the susceptible agent was drugs, including phenytoin in 1, carbamazepine in 2, and clarithromycin in 1 patient. In addition, 8.6% (3 of 35) of the patients had infectious agents in the etiology (2 patients with SJS had mycoplasma pneumonia and 1 patient had herpes simplex virus type 1 infection) (Table I).

Twelve (34.3%) patients received systemic steroids, 11 (31.4%) received intravenous immunoglobulin (IVIG), and 12 (34.3%) received systemic steroids plus IVIG for treatment. The mortality rate was 2.9% (n = 1), and morbidity was observed (lagophthalmos) in 1 (2.9%) patient (Table II). SCORTEN score of the patient who died was 4, whereas for other patients the scores were 1, 2, and 3.

Of the patients who gave consent for diagnostic tests, 11 patients underwent skin biopsy and results were found to be consistent with SJS. For most of the patients with SJS, there was suprabasal dermoepidermal detachment, vacuolization at epidermal layer, and necrosis of keratinocytes and perivascular mononuclear inflammatory infiltrate in the papillary

TABLE II. Demographic, clinical, and laboratory characteristics of patients

Characteristic	SJS/TEN (n = 35)	DRESS (n = 16)	AGEP (n = 7)
Age (y), media (IQR)	9.13 (7.05-12.85)	8.2 (1.1-13.6)	6.76 (3.02-14.22)
Sex: male	18 (51.4)	5 (31.3)	6 (85.7)
The time between drug intake and reactions (d), median (IQR)	10 (6.5-14)	11 (9-16.5)	3 (2-4)
Clinical findings			
Cutaneous findings	33 (100)	16 (100)	7 (100)
Maculopapular exanthema	26	16	—
Bullous exanthema	18	—	—
Target like lesion	17	—	—
Nikolsky signs	18	—	—
Nonfollicular, superficial pustules	—	—	7
Mucosal involvement	35 (100)	2 (12.5)	—
Oral + conjunctival	24	2	—
Oral + conjunctival + genital	8	—	—
Oral + genital	3	—	—
Lymphadenopathy	—	12 (75)	—
Laboratory findings			
Hematological abnormalities			
Leukocytosis	12 (34.3)	9 (56.3)	7 (100)
Leukopenia	4 (11.4)	4 (25)	—
Eosinophilia	—	16 (100)	—
Atypical lymphocytes	—	4 (25)	—
Hemolytic anemia	1 (2.9)	1 (6.3)	—
Thrombocytopenia	1 (2.9)	1 (6.3)	—
Elevated acute-phase reactants (ESR and CRP)	22 (62.9)	9 (56.3)	7 (100)
Abnormalities in liver function tests	12 (34.3)	14 (87.5)	1 (14.3)
Abnormalities in renal function tests	2 (5.7)	2 (12.5)	—
Positive microbiologic test	3 (8.6)	—	—
Mycoplasma pneumonia	2	—	—
Herpes simplex virus type I	1	—	—
Comorbidities			
Epilepsy	10 (28.5)	6 (37.5)	—
Asthma + allergic rhinitis	1 (2.9)	—	1 (14.3)
Epilepsy + mental retardation	1 (2.9)	—	—
Epilepsy + cerebral palsy	1 (2.9)	—	—
Acute myeloid leukemia M4	1 (2.9)	—	—
T-cell acute lymphoblastic leukemia	1 (2.9)	—	—
Pontine glioma	1 (2.9)	—	—
Ankylosing spondylitis	—	1 (6.3)	
Sickle cell anemia	—	—	1 (14.3)
Soft tissue sarcoma	—	—	1 (14.3)
Treatment			
Systemic corticosteroid	12 (34.3)	9 (56.3)	—
IVIG	11 (31.4)	2 (12.5)	—
Systemic corticosteroid + IVIG	12 (34.3)	3 (18.7)	—
Only antihistamines	—	2 (12.5)	7 (100)
Complication			
Lagophthalmos	1 (2.9)	—	—
Secondary diabetes mellitus	—	1 (6.3)	—
Mortality	1 (2.9)	—	—

CRP, C-reactive protein; *ESR*, erythrocyte sedimentation rate.
Values are n (%) unless otherwise indicated.

dermis. Patch testing was performed with ampicillin-sulbactam and with cefixime in 1 patient each, but both were negative.

Patients with DRESS

Of all the patients, 56.3% (n = 9) had definite DRESS, 31.2% (n = 5) had probable DRESS, and 12.5% (n = 2) had

possible DRESS. Antibiotics were first (50%, n = 8) and antiepileptics were second (37.5%, n = 6) most common in the etiology (Table I). Hepatitis was the most common organ involvement (14 patients; 87.5%) in patients (Table II).

Nine (56.3%) patients received systemic steroids, 2 (12.5%) patients received IVIG, 3 (18.7) patients received systemic corticosteroids plus IVIG, and 2 (12.5%) patients received only antihistamines as treatment. There was no mortality and only 1 (6.3%) patient developed secondary diabetes mellitus (Table II).

Of the patients who gave consent for diagnostic tests, the skin biopsy results of 5 patients were found to be consistent with a drug reaction. In general parakeratosis, hyperkeratosis and lymphocytic infiltration of the dermis and epidermis was noted. The patch test results of 2 patients with carbamazepine and 1 patient with cefotaxime were positive.

Patients with AGEP

In 85.7% (n = 6) of the patients, antibiotics played a part in the etiology (Table I). Although all patients received antihistamines as a treatment, topical steroids were additionally used in 3 patients (Table II). Patch testing was performed in 1 of the patients with sulbactam-ampicillin and in another patient with ceftriaxone, results for both of which were negative. In the skin biopsy of 1 patient, subcorneal pustule formation, acanthosis in the epidermis, and leukocyte-rich perivascular infiltration in the dermis were detected.

Detailed clinical and laboratory characteristics of patients are presented in Table II.

DISCUSSION

Fifty-eight patients with SCARs were evaluated in this study. Diagnosis was SJS/TEN in 60.4% of the patients, DRESS in 27.6%, and AGEP in 12%. In 93.1% of the patients, drugs were the cause of the reactions. Sequelae were seen in 2 patients. Only 1 of the patients, diagnosed with TEN, died.

Adverse drug reactions account for 6.5% of all hospital admissions.[15] The incidence of drug reactions is 6.1% in hospitalized patients, and 41.4% of these were classified as serious drug reactions, and 1.2% of them have led to death.[16] SCARs are rare in children, but potentially have morbidity and mortality, so they should be treated early and appropriately.[1] Data on pediatric patients are limited, and our study is one of the largest series of pediatric patients with SCARs.

Most common SCARs were SJS/TEN in our study group. Pathogenesis of SJS/TEN is not fully understood. The activated CD8+ lymphocytes along with natural killer cells can induce epidermal cell apoptosis in SJS/TEN via several mechanisms, which include the release of granzyme B, perforin, and FAS-FAS ligand. Chung et al[17] reported that secretory granulysin is a key molecule for the disseminated keratinocyte death in SJS-TEN.

The main causes of SJS/TEN are drugs, but some infections especially Mycoplasma and viral infections are reported as etiologic agents. Former studies have shown that drugs play a role in etiology of 75% of the cases.[18] TEN is almost entirely attributed to drugs.[1,3] Antibiotics, antiepileptics, and nonsteroidal anti-inflammatory drugs are major etiologic agents causing SJS/TEN.[3] Although data are limited in children, the most common causative drugs are reported to be antibiotics.[1] In accordance with the literature, in our study, drugs were found to be responsible in the etiology of 88.6% of the patients with SJS/TEN and antibiotics (45.7%) and antiepileptics (34.3%) were the most common drugs. However, only 2 of the 3 patients with SJS had mycoplasma pneumonia and 1 patient had herpes simplex virus type 1 infection.

Clinical manifestations are usually reported to begin in 7 to 21 days after drug exposure.[8] Latency time between the introduction of the drug and the start of SJS/TEN varies depending on the drug, which is shorter in the case of antibiotics.[19] Former studies have shown that this period is shorter for TEN than for SJS and that the symptoms generally emerge within the first 7 days of exposure.[16,20] In our study, a median of 10 days (IQR, 6.5-14 days) was found between the first dose of the drug and the onset of symptoms, with a median time of 2 days (IQR, 2-14 days) in the TEN and SJS/TEN overlap and 12 days (IQR, 7-15 days) in the SJS group, supporting the data in the literature.

Mortality is lower in children than in adults, but sequelae are relatively common.[19] The mortality rate for TEN is reported as 25% to 35% in previous studies.[6] In our study, the mortality rate was found to be 2.9% (n = 1). The diagnosis of this patient was TEN and his SCORTEN score was calculated as 4. In studies, the mortality rate for patients with a SCORTEN score of 4 is predicted as 58.3%.[19,20] Studies report incidences of serious morbidities such as lagophthalmos, blindness, pneumonia, pancreatitis, and joint contractures. However, ocular sequelae have been the most widely described.[21] Only 1 patient in our study who was diagnosed with TEN developed lagophthalmos.

Treatment is primarily supportive in SJS/TEN. Withdrawal of the culprit drug and management of symptoms are the main treatment modalities. Specific treatment in children is controversial. For the treatment of SJS/TEN, systemic steroids, IVIG, and, in persistent cases, even alternative drugs such as cyclosporine have been used.[1] A recently published meta-analysis of SJS/TEN in children found that patients treated with supportive care alone had higher mortality and morbidity rates. Patients who were treated with the combination corticosteroids and IVIG appeared to have better outcome.[22] Another meta-analysis on the efficacy of IVIG in patients with TEN reported that although IVIG exhibited a trend toward improved mortality, the evidence does not support a clinical benefit for IVIG.[23] In our study, 31.4% of patients received IVIG, 34.3% received systemic steroids, and 34.3% received systemic steroids plus IVIG. Therefore, randomized controlled trials are needed to examine specific treatments.

The exact mechanism in DRESS is not fully understood and different pathogenetic mechanisms have been implicated. Detoxification defects, slow acetylation, reactivation of human herpes virus 6 and human herpes virus 7, and predisposition in people with certain human leucocyte antigen alleles are suspected mechanisms.[4] Although DRESS may develop because of various drugs, aromatic antiepileptics are reported to be the most common cause followed by antibiotics.[24] RegiSCAR study group evaluated 117 adult cases and found that antiepileptic drugs, especially carbamazepine and lamotrigine, phenobarbital, phenytoin, and valproic acid, were responsible in 35%, allopurinol in 18%, sulfonamides and dapsone in 12%, and other antibiotics in 11%.[24] Skowron et al[25] evaluated 45 patients aged between 3 and 87 years and reported the etiologic agent as antibiotics in 51%, antiepileptics in 11%, and allopurinol in 11% of the cases. Most of the reports include mainly adults, and data about DRESS in children mostly come from the case reports. In our study, antibiotics were the most common (50%) in the etiology; 87.5% of the suspected antibiotics were in the beta-lactam group, and 12.5% were in the macrolide group. In 37.5%

of the cases, antiepileptics were suspected as the etiology, 83.3% of which were aromatic types.

In our study, female children constitute 68.8% of patients diagnosed with DRESS. Similarly, studies in the literature report that DRESS was observed to be more prevalent among women than among men.[24] The average time period between drug intake and symptoms was reported in the literature as 22 days, with a varying duration based on the etiologic agent.[24] Most often the interval is between 2 and 6 weeks after exposure; however, symptoms may occur more quickly and could be more severe in subsequent exposures. In our study, the median time between drug use and the onset of symptoms was found to be a median of 11 days. Particularly in DRESS due to antibiotics, the latent period is shown to be much shorter.[25] This may be the reason for a shorter time interval after drug exposure in our study because antibiotics were the most common cause in our patients.

Many organs can be affected including liver, kidney, heart, lung, brain, thyroid, and pancreas. Visceral involvement often determines severity. The liver is reported to be the most frequently affected organ (60%-80%), and renal failure is seen in 10% to 30% of the cases.[26] In our study, liver was the most frequently affected internal organ in 14 patients and kidney involvement was observed in 2 patients. Morbidity rates in the literature vary between 5.8% and 11.5% in patients with DRESS.[25] One of our patients developed secondary diabetes mellitus during the disease.[27] The mortality rate is reported to be about 10% for DRESS.[5] In our study, mortality was not observed.

Diagnostic tests, especially patch tests, are performed to identify the causative drug.[13] In a study on adult patients, 72% of cases with carbamazepine-induced DRESS and 14.3% of cases who had reaction with phenytoin had a positive patch test result.[28] The patch test results of 2 patients with carbamazepine and 1 patient with cefotaxime were positive in our study.

Although there is no consensus among the studies, the main treatment strategy is the immediate discontinuation of the suspected drug and administration of systemic steroid treatment.[1] Other treatment modalities such as IVIG, plasmapheresis, cyclophosphamide, and cyclosporine have also been used in DRESS.[1] Treatment strategy should be modulated according to the severity of internal organ involvement. In our study group, 56.3% of patients received systemic steroids, 15.5% received IVIG, 18.7% received systemic corticosteroids plus IVIG, and 12.5% received antihistamine treatment alone.

Limited data exist in the literature regarding children with AGEP. AGEP can be caused by drugs or both viral and bacterial infections especially in children.[29] Antibiotics and in particular aminopenicillins have been shown to be the most common (90%) etiologic agents.[29] Accordingly, betalactam antibiotics are the most common responsible drugs (85.7%, n = 6) in our study.

There is no specific treatment for AGEP. Symptomatic treatment (antihistamines, topical steroids, moisturizers) is recommended. There are studies showing that topical steroids reduce the length of hospital stay. However, the effect of systemic steroids has not been determined.[30] In our study, all patients diagnosed with AGEP received antihistamines, whereas topical steroids were additionally used in 3 patients. The median treatment period was 7 days (IQR, 7-14 days) and no morbidity or mortality was observed, which is consistent with the cases in the literature. However, a 17% rate of internal organ involvement was shown in 1 study.[31]

There are some limitations of our study. All patients in our study were diagnosed objectively using the standard scoring systems. However, the absence of skin biopsy and/or patch testing for suspected drugs in most patients may be considered a limitation. Consent could not be obtained from the parents of most patients for skin biopsy or patch testing with the suspected drug/drugs. In addition, *in vitro* tests that can be used could not be carried out.

In conclusion, a high index of suspicion should be maintained to make a rapid diagnosis in SCARs. There is no consensus yet on the topic of effective systemic and topical treatments for SCARs. Up until now, controlled clinical trials have not been performed for any of the proposed treatments. In particular, there is not enough data on SCARs in children. Therefore, prospective, multicenter, and randomized controlled studies on the topics of diagnosis, monitoring, and, in particular, treatment of SCARs in children should be carried out to reduce morbidity and mortality rates and to identify new treatment modalities based on newly defined pathophysiological mechanisms. The most common responsible agent was antibiotics in our study. Thus, rational antibiotic use may help to decrease the frequency of SCARs.

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