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Recurrence and Outcomes of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Children

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KEY WORDS

Stevens-Johnson Syndrome, toxic epidermal necrolysis, children, adverse drug reactions

ABBREVIATIONS

SJS—Stevens-Johnson syndrome
TEN—toxic epidermal necrolysis
BSA—body surface area
IVIg—intravenous immunoglobulin
HSC—Hospital for Sick Children
CHB—Children's Hospital Boston

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WHAT'S KNOWN ON THIS SUBJECT: Stevens-Johnson syndrome and toxic epidermal necrolysis are life-threatening complications of drug therapy. Both conditions are associated with serious sequelae and a high mortality rate in adults, but few data are available from children.

WHAT THIS STUDY ADDS: The mortality rate was lower than that reported for adults, but half of affected children suffered long-term complications. The recurrence rate of Stevens-Johnson syndrome was high, which suggests vulnerability and potential genetic predisposition. Standardized treatment guidelines are lacking, and management differed significantly between participating institutions.

abstract

OBJECTIVES: To report clinical course, etiology, management, and long-term outcomes of children suffering from Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

METHODS: We conducted a study of all pediatric patients with SJS or TEN admitted between 2000 and 2007 to the Hospital for Sick Children and Children's Hospital Boston, and particular attention was paid to clinical manifestations, etiology, mortality, and long-term outcomes.

RESULTS: We identified 55 cases of SJS ($n = 47$), TEN ($n = 5$), or SJS/TEN overlap syndrome ($n = 3$). Drugs were identified as the most likely etiologic agent in 29 children (53%); antiepileptic drugs were the most common agents ($n = 16$), followed by sulfonamide antibiotics ($n = 7$) and chemotherapy drugs ($n = 2$). Acute *Mycoplasma pneumoniae* infection was confirmed in 12 children (22%), and herpes simplex virus was confirmed in 5 children (9%). Treatment regimens differed significantly between participating sites and included systemic antimicrobial agents (67%), systemic corticosteroids (40%), and antiviral drugs (31%). Intravenous immunoglobulin was administered to 21 children (38%), of whom 8 received concomitant systemic corticosteroids. Ten children (18%) had recurrence of SJS up to 7 years after the index episode, and 3 experienced multiple recurrences. Twenty-six children (47%) suffered long-term sequelae that mostly involved the skin and eyes.

CONCLUSIONS: Mortality rate in children was lower than that reported in adults, but half of affected children suffered long-term complications. The recurrence rate of SJS was high (1 in 5), which suggests vulnerability and potential genetic predisposition. In the absence of standardized management guidelines for these conditions, treatment regimens differed significantly between participating institutions. *Pediatrics* 2011;128:723–728

Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening conditions that represent different intensities along a spectrum of severe cutaneous adverse reactions to drug therapy. Both conditions are associated with significant morbidity and mortality (up to 5% in SJS and >20% in TEN in adults).[1–6]

The SJS/TEN spectrum is characterized by widespread keratinocyte apoptosis, which results in extensive epidermal detachment.[7] SJS is defined as epidermal detachment of <10% body surface area (BSA) and TEN as >30% BSA; cases with skin involvement between 10% and 30% are classified as SJS/TEN overlap. Severe mucous membrane involvement is common. SJS and TEN occur in both genders and all races and ages. The estimated incidences for SJS and TEN in the general population range from 1.2 to 7.0 cases and 0.4 to 1.2 cases per million people per year, respectively.[6,8–12] The exact pathogenesis of SJS and TEN is unknown. The clinical course is typically prolonged, even after drug discontinuation.[1,13]

At present, there are no evidence-based standardized treatment guidelines for SJS or TEN. Withdrawal of the suspected causative agent and supportive therapy are the mainstays of current treatment. Specific therapeutic strategies are controversial in pediatric patients[14] and include systemic corticosteroids and, more recently, the use of intravenous immunoglobulin (IVIg).[15–17] Treatment strategies are also controversial in adults, in whom IVIg[18,19] as well as immunosuppressive therapies such as cyclosporine, etanercept, and plasmapheresis have been used.[2,14,20]

We report our experience with SJS and TEN at 2 large tertiary-care pediatric centers. We describe the etiologic agents, clinical manifestations, and management of these cases and focus on the long-term sequelae and recurrences of these life-threatening conditions in children.

METHODS

We analyzed the health records of all children who presented or were transferred to the emergency department and admitted for SJS, TEN, or SJS/TEN overlap syndrome between January 1, 2000, and December 31, 2007, at 2 pediatric tertiary-care hospitals: the Hospital for Sick Children (HSC) and Children's Hospital Boston (CHB). Charts were identified by using the *International Classification of Diseases, 10th Revision* (ICD-10) discharge code L51.1 for SJS and ICD-10 code L51.2 for TEN. Cases were selected by using the widely accepted classification criteria reported by Bastuji-Garin et al.[21] To confirm diagnoses, charts were manually reviewed by an investigator who had not taken part in the initial selection. For completeness, the follow-up clinic records of all SJS and TEN cases were reviewed and cross-referenced with the index list. Eligible patients included children aged 0 to 21 years who were admitted to the hospital with a diagnosis of SJS, TEN, or SJS/TEN overlap that was made in real time by the respective pediatric dermatology teams. Patients with other, usually milder, conditions (erythema multiforme minor, erythema multiforme major, and bullous erythema multiforme) were excluded.

Data were extracted manually from hospital charts by using a standardized data collection form that had been agreed on by the research groups in both participating institutions. Medical records were reviewed to identify the following: demographic characteristics, medical history, previous drug exposures, most likely etiologic agent, clinical course (eg, % BSA involved, skin dyspigmentation, genital involvement, body temperature, laboratory data [including bacterial cultures, viral serology, and pathologic description], need for surgical debridement/intervention, final diagnosis [SJS, TEN, or SJS/TEN overlap]) and short-term and long-term sequelae including survival and recurrences.

Analyses of descriptive statistics were conducted for the variables of interest: continuous variables (mean, median, SD, and quartiles) and categorical variables (frequency and percentage). Where appropriate, 95% confidence intervals were calculated. Comparisons were analyzed with the Student's t test, Mann-Whitney U, χ^2, Pearson product moment correlation, and Spearman rank analysis by using SPSS 8 statistical software (SAS Institute, Cary, NC).

RESULTS

Fifty-five children (35 boys; 35 patients at CHB) were admitted to both institutions and had a discharge diagnosis of SJS (85%), TEN (9%), or SJS/TEN overlap (6%) during the 8-year study period. Mean age at presentation was 9.6 ± 4.8 years (range 0.5–21 years). Twenty-three children (42%) were previously healthy and 32 (58%) had an underlying disease. The demographic characteristics of all study patients are summarized in Table 1.

Adverse reaction to medication was the most likely causative factor in 29 children (53%); anticonvulsants were the most commonly implicated (16 children; 29%), followed by sulfonamide antimicrobial agents (7 children; 13%), as shown in Table 1. Infection was identified as the most likely cause in 17 children (31%); acute *Mycoplasma pneumoniae* infection was documented in 12 children (22%) and herpes simplex virus in 5 children (9%). Etiology could not be reliably determined in 10 children (18%). Fifteen children (27%) underwent skin biopsy to confirm the diagnosis.

TABLE 1 Demographic and Baseline Characteristics and Presumed Etiology of SJS, SJS/TEN Overlap, and TEN in 55 Children

	Total Cohort ($N = 55$)
Demographic characteristic	
Gender, male, *n* (%)	35 (64)
Male/female ratio	2.4:1
Age at diagnosis, mean ± SD (range), y	9.6 ± 4.8 (0.5–21)
Ethnic origin ($N = 36$ known), *n* (%)	
White	22/36 (61)
Asian	7/36 (19)
Black	5/36 (14)
Hispanic	2/36 (6)
Baseline health, *n* (%)	
Healthy	23 (42)
Baseline disease, *n* (%)	32 (58)
Epilepsy	12 (38)
Psychiatric disorders	6 (19)
Malignancy	4 (12)
Asthma	3 (9)
Pneumonia	2 (6)
Autoimmune disease	1 (3)
Severe combined immunodeficiency	1 (3)
Crohn disease	1 (3)
Asperger syndrome	1 (3)
Ocular albinism	1 (3)
Etiology	
Drugs, *n* (%)	29 (53)
Antiepileptic agents	16 (29)
Carbamazepine	5 (9)
Lamotrigine	4 (7)
Phenobarbital	3 (5)
Ethosuximide	1 (2)
Oxcarbazepine	1 (2)
Phenytoin	1 (2)
Zonisamide	1 (2)
Antibiotics	11 (20)
Sulfonamide	7 (13)
Sulfamethoxazole trimethoprim	6 (11)
Sulfamethoxazole erythromycin	1 (2)
Other	4 (7)
Azithromycin	2 (4)
Amoxicillin	2 (4)
Chemotherapy	1 (2)
Infections, *n* (%)	17 (31)
Mycoplasma	12 (25)
Herpes virus	5 (9)
Undetermined	10 (18)

In addition to supportive care provided to all children (eg, maintenance of fluid balance and electrolytes, nutritional support, mucosal care [including amniotic membrane treatment for ocular involvement], topical skin care, and adequate analgesia), additional therapies during hospital admission included systemic antibiotics (67%), antiviral medications (31%), and systemic corticosteroids (40%) (Table 2). IVIg, at total doses ranging from 1 g/kg to 5 g/kg, were administered to 21 children (38%). Eight children (15%) were administered combined therapy with systemic corticosteroids and IVIg. Treatment modalities differed significantly between the 2 participating institutions (Table 2).

TABLE 2 Management of SJS, SJS/TEN Overlap, and TEN Cases

	Total Cohort ($N = 55$), *n* (%)	CHB ($n = 35$), *n* (%)	HSC ($n = 20$), *n* (%)	*P*
Supportive care	55 (100)	35 (100)	20 (100)	1.000
Systemic antibiotics	37 (67)	18 (51)	19 (95)	0.001
Systemic antivirals	15 (31)	7 (20)	8 (40)	0.527
Systemic corticosteroids	22 (40)	13 (37)	9 (45)	0.582
IVIg	21 (38)	8 (23)	13 (65)	0.004
Corticosteroids plus IVIg	8 (14)	2 (6)	6 (30)	0.021

Twenty-six children (47%) suffered long-term sequelae, mostly involving the skin and eyes, as well as rarer complications (Table 3). Long-term sequelae were equally distributed between the 2 centers (12 of 23 patients with skin complications and 8 of 15 patients with ophthalmic complications were from CHB). Children with ophthalmic complications were admitted for significantly longer periods than those without them (38.2 ± 15.4 days vs 17.6 ± 10.1 days, respectively; $P = .04$; HSC). Univariate odds ratios for ocular sequelae in patients who received IVIg were significantly higher compared with those for patients who did not receive IVIg. Results of additional analysis performed by using logistic regression modeling, including IVIg treatment, systemic corticosteroid treatment, age, and diagnosis (SJS, TEN, or SJS/TEN overlap) confirmed an association between IVIg use and increased incidence of ocular sequelae (corrected odds ratio: 46.57; 95% confidence interval: 5.34–1195.8; $P < .01$). No exposure to systemic corticosteroids, age, and diagnosis were associated with ocular sequelae in the logistic regression model. One child in our series (2%) died from graft-versus-host disease secondary to bone marrow transplantation for severe combined immunodeficiency. Ten children with initial SJS (18% of total group, 21% of SJS group) had recurrent SJS episodes, and 3 (5%) experienced multiple recurrences (Table 4).

TABLE 3 Outcome of 55 Children with SJS, SJS/TEN Overlap Syndrome, and TEN

	Total Cohort ($N = 55$), *n* (%)
Long-term sequelae	25 (45)
Skin sequelae (eg, hypopigmentation, scarring)	23 (42)
Eye sequelae (eg, uveitis, keratitis, corneal defects, chronic conjunctivitis)	15 (27)
Phimosis	2 (4)
Sclerosing cholangitis	1 (2)
Bronchiolitis obliterans	1 (2)
Stridor	1 (2)
Venous thrombosis	1 (2)
Recurrence of SJS	10 (18)
Recurrence of TEN	0 (0)
Mortality	1 (2)

DISCUSSION

SJS and TEN are uncommon but life-threatening conditions in children. To date, with the exception of a single case-control study,[4] these illnesses have been addressed in the literature in only a few case reports and small series of pediatric cases.[17,22–25] The exact morbidity, mortality, and predictors for poor outcome in pediatric patients cannot be derived from current

TABLE 4 Recurrence of SJS Episodes in 10 Patients

Patient	Gender	Ethnic Origin	Episode	Age, y	Time to Recurrence, y[a]	Etiology
1	Male	Asian	First	8.4	—	Sulfonamide
			Second	13.0	4.6	Mycoplasma (IgM$^+$)
			Third	15.3	2.3	Unknown
2	Female	NA	First	10.9	—	Mycoplasma (IgM$^+$)
			Second	13.8	2.9	Mycoplasma (IgM$^+$)
3	Male	White	First	14.9	—	Herpes simplex virus
			Second	17.5	2.6	Herpes simplex virus
			Third	17.7	0.2	Herpes simplex virus
4	Female	White	First	14.0	—	Phenytoin
			Second	15.3	1.3	Lamotrigine
5	Male	NA	First	15.0	—	Carbamazepine
			Second	21.0	6.0	Zonisamide
6	Male	White	First	10.6	—	Mycoplasma (IgM$^+$)
			Second	10.8	0.2	Herpes simplex virus
7	Male	White	First	11.0	—	Mycoplasma (IgM$^+$)
			Second	12.7	1.7	Mycoplasma (IgM$^+$)
			Third	13.8	1.1	Mycoplasma (IgM$^+$)
8	Male	White	First	11.8	—	Amoxicillin
			Second	12.5	0.7	Mycoplasma (IgM$^+$)
9	Male	Hispanic	First	14.3	—	Pneumonia
			Second	14.7	0.4	Unknown
10	Female	Asian	First	14.5	—	Lamotrigine
			Second	14.8	0.3	Unknown

NA indicates not available; IgM, immunoglobulin M.
[a] Time from previous episode.

literature, in contrast to a relatively large body of literature in adults, in whom the mortality rate ranges from 5% in SJS to >20% in TEN.[3–6] In our series, 1 child (2%) died from complications of TEN and graft-versus-host disease related to the underlying illness.

SJS is frequently and TEN is most commonly drug induced. More than 100 drugs have been associated with these conditions, but only a small number are responsible for the majority of cases, especially in children.[4,6,10,26] Common triggers include anticonvulsants, sulfonamides, and oxicam nonsteroidal antiinflammatory drugs, with drug-specific incidences ranging from 1 in 10 000 to 1 in 100 000 new drug courses.[4,6,10,11,26–29] Other reported triggers of SJS include chemicals, immunizations, *M pneumoniae*, and viral infections.[13,23] Our cohort demonstrated a similar etiologic distribution. Most children developed SJS or TEN after drug exposure, mostly to anticonvulsants and sulfonamide antibiotics, or infections, and approximately half of the affected children had an underlying disease.

Almost half of affected children suffered from long-term sequelae, mainly skin, including genital scarring, and ocular manifestations (Table 3), which suggests commonality of significant long-term complications associated with these conditions in children. To the best of our knowledge, the incidence and extent of long-term sequelae after SJS or TEN have not been well studied in adults or previously described in children. We suggest that children suffering from SJS or TEN should be closely monitored for possible long-lasting complications.

In the absence of consensus management guidelines, treatment modalities differ significantly among centers, as shown in our 2 participating centers. For example, at HSC two-thirds of children were treated with IVIg and approximately one-third received a combined regimen of IVIg and systemic corticosteroids. At CHB, however, only 23% were treated with IVIg and only 6% with a combined therapy (Table 2). Similar findings were noted for the use of systemic antibiotics, which were administered to almost all HSC patients and only half of those treated at CHB.

Data from scattered case series suggest that IVIg therapy may lower morbidity and mortality rates associated with SJS and TEN.[15,16,19] In our series, children who were administered IVIg had a higher incidence of ocular complications compared with those who did not. However, the retrospective design of the study prevents us from reaching inferences about causality. It is probable that sicker children, with a higher risk for development of ophthalmic and other complications, were more likely to be administered IVIg compared with patients with milder disease. This is supported by the longer length of admission of children with ophthalmic complications compared with those without them. The issue of optimal treatment of pediatric SJS and TEN, including the role of IVIg therapy, should be further investigated.

Another novel finding was the high rate of recurrence of SJS in children. One in 5 had been admitted at least once for recurrent SJS episodes. A third of these patients had multiple SJS episodes during the study period. All recurrent SJS episodes were distinct events leading to admissions and occurred between 2 months and up to 7 years after the index episode (Table 4). Etiology was reliably determined in the majority of cases. It is interesting that recurrent *M pneumoniae* infections were responsible for recurrent SJS in only 2 of 10 cases. In 2 additional cases, recurrent SJS was clearly attributable to exposure to anticonvulsants of different drug classes (phenytoin and lamotrigine in 1 patient, and carbamazepine and zonisamide in the

other; both had confirmed negative infectious serologies). Recurrence, especially multiple episodes, of such a rare event in almost 1 in 5 children is unlikely coincidental and strongly suggests long-lasting vulnerability and potential genetic predisposition. Such mechanisms have been shown in Asian patients with the HLA-B*1502 genotype, who have a strong tendency to develop carbamazepine-induced SJS.[30] Further study into the pharmacogenetic mechanisms leading to recurrent SJS is warranted to identify those at risk and to shed a light of potential pathophysiologic mechanisms that underlie primary and recurrent SJS and may serve as new therapy targets.

The main limitations of our study were its retrospective design and the limited usefulness for providing definite proof of causality for suspected agents beyond temporal relationship and laboratory support. However, this limitation is shared by virtually all SJS and TEN studies, because these patients are too sick to be rechallenged with suspected drugs. For infection-related SJS, nature allows us to be confident regarding causality. Patients with infection-related SJS demonstrate recurrent clinical symptomatology after reinfections with similar pathogens (*M pneumoniae* and HSV). We were unable to apply the SCORTEN (Score of Toxic Epidermal Necrosis) severity scale to our patients because it has not been validated in children, and several of its parameters are not applicable to patients in the pediatric age group.

CONCLUSIONS

In this study of 55 children with SJS or TEN, we found that the mortality rate was lower than that reported in adults, but nearly half of the affected children suffered long-term complications, including debilitating ophthalmic manifestations. The recurrence rate of SJS was high, and recurrence occurred in 1 in 5 affected children, up to 7 years after the index episode. Treatment modalities differed significantly between the 2 participating institutions, and future prospective studies are needed to better characterize optimal treatment strategies.

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QUESTIONING THE REALITY OF THE "JULY EFFECT": *I had just logged onto my favorite social networking site and was immediately reminded that it's July, a time when hospitals are supposedly most dangerous. Several people had posted warnings that "whatever you do, don't come to a hospital this month." Statements such as this perpetuate the grip that the rumored "July effect" has on public opinion. The July effect refers to the supposed increase in medical error and hospital mortalities associated with the arrival of freshly minted doctors to the resident team. However, according to* The New York Times *(Health: July 4, 2011), the body of research regarding the existence of such an effect is, at best, mixed. In 2 separate studies that examined the outcomes in surgical and cardiac care patients conducted at the University of Michigan and the University of Minnesota, respectively, no significant rise in medical mismanagement was reported. However, another study in* The Journal of General Internal Medicine*, found a 10% increase in fatal medication administration errors. Adding to the controversy surrounding this topic,* The New York Times *published an update (Health: July 11, 2011) reviewing the most recent study of this phenomenon. Although there are inconsistencies in the 40 studies reviewed, researchers concluded that death rates in the hospital are 8% higher during July. The month of July is an exciting time in a new physician's training and offers the opportunity to continue his or her medical education with increased patient-management responsibilities. Still, I cannot help but question the current existence of a July effect. With ever-changing residency regulations resulting in greater supervision by an attending physician, it seems as though July would be a time during which hospital staff are highly attentive to patient care, order-checking, and monitoring. Although the jury is still out on the existence of the July effect, it might be beneficial to reassure the public that treatment at a teaching hospital includes not only the care of eager, well-trained, enthusiastic young physicians but seasoned attending physicians who have weathered many Julys in the past.*

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