

Clinical characteristics of childhood erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in Taiwanese children

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Erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are mucocutaneous diseases associated with significant morbidity and mortality. This study compared childhood EM, SJS and TEN in terms of clinical courses, laboratory data, etiologies and outcomes in Taiwan. The initial laboratory findings, clinical presentations, etiologies and subsequent clinical courses of 30 patients with a diagnosis of EM, SJS or TEN, who were admitted between 1995 and 2003 at National Taiwan University Hospital were included and analyzed. There were 19 cases of EM, 8 cases of SJS, 2 cases of SJS/TEN and 1 case of TEN. The most common etiology in EM was infection (84.2%), and the most common implicated organism was *Mycoplasma pneumoniae* (42.1%). In contrast, 75% of SJS and 100% of TEN were induced by drugs. The most common offending drug was carbamazepine. Those patients with underlying diseases had more protracted courses and longer hospitalization stays. No mortalities were found in our cases. Early short-term steroid equivalent to 1-2 mg/kg/day of prednisolone for 3-5 days was used in 87.5% of SJS patients, without any significant side effects. Those with poor responsiveness to steroids and protracted courses were treated with additional intravenous immunoglobulin (IVIG) [1 g/kg/day], with satisfactory results. Early ophthalmic consultations were performed in all cases. No ocular complications were found in our cases. In conclusion, EM, SJS and TEN were associated with significant morbidity. Early ophthalmic consultations and withdrawal of the offending medication was necessary. Early short-term use of steroids in SJS showed promising results without significant side effects. The additional IVIG in those who had a poor response to steroid treatment may be helpful.

Key words: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, treatment outcome

Erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute mucocutaneous syndromes that are related to hypersensitivity reaction to various agents including drugs and infections. Histopathology of EM shows limited involvement at the dermo-epidermal junction, while SJS/TEN show full thickness necrosis of the epidermis [1]. Moreover, there is evidence that the inflammatory infiltrates of EM and TEN are strikingly different, with the former having higher-density T lymphocyte infiltrates and the latter having poorer cell infiltrate with macrophages and dendrocytes [2].

EM is divided into EM major and EM minor. EM minor is a self-limited process that is characterized by acute onset of acral and symmetric erythematous papules evolving into the typical target lesion. Mucosal

involvement is limited. It is most commonly caused by infection, especially herpes simplex virus (HSV) [3] and *Mycoplasma pneumoniae* in children. EM major is equivalent to SJS in most classification schemes. SJS is characterized by high fever, pronounced constitutional symptoms, and widespread blistering and erosions on 2 or more mucous membrane surfaces. Almost 100% of patients with SJS have stomatitis and 90-100% have conjunctivitis [4]. Fifty percent of SJS is drug-induced; anticonvulsants, penicillin, and sulfonamides account for 91% of cases. The mortality rate is about 5% [5]. SJS can evolve into life-threatening TEN. Medications are also the most common provoking factor in TEN (>80%) [5], which is characterized by sheet-like loss of epidermis and raised flaccid blisters, which spread with pressure (Nikolsky's sign). The disorder is also associated with a significant mortality rate of about 30%. Sepsis and hypovolemia are the principal cause of death. Early ophthalmologic consultation is important for SJS and TEN, since ocular sequelae affect 35% of patients

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who survive TEN and a smaller percentage of those with SJS [6]. Studies have also revealed that human leukocyte antigen phenotype B12 is associated with a 3-fold increase in the risk of TEN [7].

The aim of this study is to review the clinical experience of manipulating bullous EM, SJS and TEN. The laboratory features, causative factors, treatment, morbidity and mortality of these diseases are also analysed.

Patients and Methods

Our study performed a retrospective analysis of the cases of bullous EM, SJS and TEN at National Taiwan University Hospital (NTUH) between 1995 and 2003. The charts of all patients with an admitting or discharge diagnosis of bullous EM, SJS or TEN during this period were reviewed.

Thirty patients were identified with a diagnosis of SJS, EM or TEN while visiting the department of pediatrics and internal medicine between 1995 and 2003. Clinical parameters such as age, gender, relevant past medical history, duration of fever, total hospital stays period, time to response to therapy, antecedent use of medications, distribution of cutaneous lesions, presence and extent of mucous membrane involvement, presence of Nikolsky's sign, presence of ocular involvement, laboratory data (complete blood count, C-reactive protein, glutamate-oxaloacetate transaminase/ glutamate-pyruvate transaminase [GOT/GPT]), blood urea nitrogen (BUN)/creatinine, sodium/potassium/

chloride, infectious disease data (cultures, cold agglutinins, viral titers including *Mycoplasma*, HSV and Epstein-Barr virus [EBV]), treatment protocol (corticosteroid, antihistamines, intravenous immunoglobulin [IVIG] use), complications and mortality were collected. "Time to response" was defined as the objective observation of the interruption in the progression of the disease.

Patients were separately categorized according to the classification system for bullous EM proposed by Bastuji-Garin et al [8].

Cases were considered to be drug-related if the patient was exposed to the agent within a few weeks prior to the onset of the rash. Cases were considered related to infectious agents if the infectious process was noted to have taken place within 1 week prior to the onset of the rash. Cases were considered to be definitely *M. pneumoniae*-related infection only if *Mycoplasma* immunoglobulin M titers were available.

Results

Within the period of 1995 to 2003, 30 patients were diagnosed with EM, SJS, SJS/TEN or TEN. All patients were categorized according to the classification of severe bullous EM by Bastuji-Garin et al [8]. There were 19 patients diagnosed with EM, 8 with SJS, 2 with SJS/TEN, and 1 with TEN (Fig. 1). The mean age of onset in EM, SJS, and TEN was 4.02 years, 12.5 years, and 12 years, respectively. The mean laboratory parameters of EM, SJS, and TEN are shown in Table 1. The

Table 1. Mean laboratory parameters of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)

	EM (n = 19)	SJS (n = 8)	TEN (n = 1)
Age (years)	4.02 (range, 3 months-17 years)	12.5 (range, 2.8-18 years)	12
M:F	8:11	5:3	
Duration of fever (days)	4.68	3.1	4
White blood cells (μ L)	9960 (4640-18,270)	9136 (3000-19,200)	5080
Hemoglobin (g/dL)	11.43	12.5	11
Platelets (μ L; \times 1000)	269.6	238.2	109
C-reactive protein (mg/dL)	2.90	3.03	1.2
Blood urea nitrogen (mg/dL)	9.08	11.35	21.3
Creatinine (mg/dL)	0.48	0.7	0.7
Sodium (mmol/L)	137.5	138.3	136
Potassium (mmol/L)	4.07	4.3	4.9
Chloride (mmol/L)	105.9	103.5	102
GOT (U/L)	37.7	41.9	81
GPT (U/L)	32.1	82.4	48
Time to response (days)	2.3 (range, 1-3)	3.75 (range, 1-7)	7
Total hospital stays (days)	5.9 (range, 3-11)	10.12 (range, 3-19)	10

Abbreviations: GOT = glutamate-oxaloacetate transaminase; GPT = glutamate-pyruvate transaminase

Table 2. Treatment of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN

Diagnosis	Treatment	No. of cases (%)	Total (%)
EM	Steroid + supportive care	2 (10.5)	19 (100)
	Steroid + antihistamine + supportive care	3 (15.8)	
	Antihistamine + supportive care	7 (36.8)	
	Steroid + antibiotics	1 (5.26)	
	Antihistamine + antibiotics	3 (15.8)	
	Antibiotics + supportive care	2 (10.5)	
	IVIg + steroid	1 (5.26)	
SJS	Steroid + supportive care	2 (25)	8 (100)
	Steroid + antihistamine + supportive care	3 (37.5)	
	Antihistamine + supportive care	1 (12.5)	
	IVIg + steroid	2 (25)	
TEN	Antihistamine + surgical debridement + supportive care	1 (100)	1 (100)
SJS/TEN	Steroid + antihistamine + supportive care	1 (50)	2 (100)
	IVIg + steroid	1 (50)	

Abbreviation: IVIG = intravenous immunoglobulin

mean white blood cell and BUN/creatinine of EM, SJS, and TEN were within normal limits. GOT (U/L)/GPT (U/L) was higher in SJS and TEN than in EM (41.9/82.4 and 81/48 vs 37.7/32.1). Time to response after initiating therapy was 2.3 days, 3.75 days, and 7 days in EM, SJS, and TEN, respectively. Total hospital stay was 5.9 days, 10.12 days, and 10 days in EM, SJS, and TEN, respectively (Table 1).

Overall, 46.7% (14 patients) had mucous membrane involvement. Oral lesions occurred in over 95% of the cases that had mucous membrane involvement, ranging from erosion or bullae to involvement of the entire buccal mucosa, pharynx, tongue and lips. Anogenital lesions were documented in 28.6% of total patients with mucous membrane involvement. Other mucosal lesions, such as those in the esophagus, colon, and nasal cavities, were rare. Ocular involvement was noted in 23.3% of total patients. Hemorrhagic conjunctivitis, corneal ulceration, conjunctivitis with purulent discharge, blepharitis, scleritis, and photophobia were documented. Other complications, such as sepsis, skin infection, hepatitis, and pigmentation changes (hyperpigmentation or hypopigmentation) were also found.

The treatment protocol is summarized in Table 2. In EM, 7 patients (36.8%) were treated with the steroid equivalent to prednisolone 1-2 mg/kg/day, in a short course (≤ 3 days) due to progressive mucosal involvement, since EM was most commonly related to infection such as *M. pneumoniae*. Clarithromycin was also prescribed if the *Mycoplasma* titer was elevated. Thirteen patients (68.4%) were treated with antihistamines and supportive care (Table 2). One patient was treated with additional IVIG (1 g/kg/day) during

hospitalization due to uncontrolled infection, persistent leucopenia, and young age. In SJS, 7 patients (87.5%) were treated early with steroid treatment equivalent to prednisolone 2 mg/kg/day for 3-5 days. Two patients (25%) were treated with additional IVIG (1 g/kg/day) due to a poor response to steroid treatment and progression of the disease. In SJS/TEN, 2 patients (100%) were treated with the steroid treatment equivalent to prednisolone 2 mg/kg/day (3-5 days). One patient was treated with additional IVIG due to a poor response to the steroid treatment and progression of the disease. There was only 1 patient with the diagnosis of TEN in our study, and he was treated in the surgical department. An extensive area of bullae was found over trunk, so surgical debridement was performed. Those areas were then covered with wet dressings, and the patient was treated as a burn patient. No steroid was used in this case.

Sixteen patients (84.2%) were affected by infectious agents in EM (Fig. 1 and Table 3). The most common

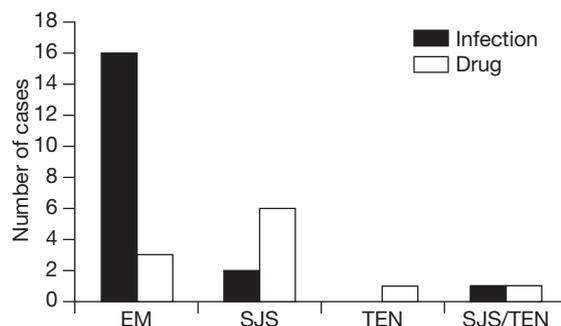


Fig. 1. Etiology of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN.

Table 3. Etiology of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN

Diagnosis	Etiology subtype	Etiology		Total (%)
		Infection (%)	Drug (%)	
EM	Herpes simplex virus	1 (5.26)	0	19 (100)
	<i>Mycoplasma</i>	8 (42.1)	0	
	Epstein-Barr virus	1 (5.26)	0	
	Adenovirus	1 (5.26)	0	
	Cefuroxime axetil	0	1 (5.26)	
	Unknown	5 (26.3)	2 (10.5)	
	Total	16 (84.2)	3 (15.8)	
SJS	Herpes simplex virus	1 (12.5)	0	8 (100)
	Carbamazepine	0	1 (12.5)	
	Valproate sodium	0	1 (12.5)	
	Lamotrigine	0	1 (12.5)	
	Unknown	1 (12.5)	3 (37.5)	
	Total	2 (25)	6 (75)	
TEN	Carbamazepine	0	1 (100)	1 (100)
	Total	0	1 (100)	
SJS/TEN	<i>Mycoplasma</i>	1 (50)	0	2 (100)
	Carbamazepine	0	1 (50)	
	Total	1 (50)	1 (50)	

infectious agent was *M. pneumoniae*, which accounted for 8 cases (42.1%) [Table 3]. Other infectious agents, including HSV, EBV, and adenovirus, were also found. No identified agents were found in 7 cases (36.8%) [Table 3]. Only 2 cases (25%) were caused by infectious agents, while 6 cases of SJS (75%) were caused by drugs. The most common drug was anticonvulsants, which accounted for 3 cases (37.5%) [Table 3]. One case (50%) was caused by infection, while the other (50%) was caused by drugs such as carbamazepine in SJS/TEN (Table 3). The 1 case of TEN (100%) was caused by drugs such as carbamazepine (Table 3).

Discussion

Bullous EM, SJS and TEN are relatively uncommon diseases in the pediatric ward. The incidence of EM has been estimated at between 0.01-1%. The incidences of SJS and TEN have been estimated at 0.4 to 1.2 and 1.2 to 6 per million people per year, respectively [5]. The mortality rates of SJS and TEN are 5% and 30%, respectively [5]. EM is often caused by infection: most commonly herpes simplex followed by *M. pneumoniae* [9]. In our study of EM, 16 cases (84.2%) were caused by infection, and 8 of those cases (42.1%) were caused by *M. pneumoniae* (Table 3). Only 3 cases of EM (15.8%) were caused by drugs. No offending organisms were identified in 5 cases of EM (26.3%); the causes of EM in those cases may be a combination of drug

and infection. In addition, we found that drug-induced EM tended to have a more severe course than infection-induced EM. The mainstay treatment of EM in our study was withdrawal of the offending drugs or treating the underlying infection, such as *M. pneumoniae* or herpes simplex, and supportive care, including antihistamine prescription. It so happened that each individual lesion developed and then resolved over the course of 1 week. In those with progressive mucosal involvement, we prescribed short-course steroid treatment. In contrast to EM, 75% of SJS (6 cases) and 100% of TEN (1 case) were caused by drugs rather than infection. Anticonvulsants, penicillin, and sulfonamides accounted for 91% of the drugs in SJS [1]. In our study, the most common offending drugs in SJS were anticonvulsants, and they contributed to 3 cases (37.5%) of SJS (Table 3). The onset of drug-related cases of EM, SJS, and TEN was typically 2 weeks after initiating therapy or shorter if the patient had previously been exposed to the medication [1,5]. Rzany et al had suggested that SJS and TEN are associated with short-term therapy with phenytoin, phenobarbital, and carbamazepine [10]. Lamotrigine has the potential for inducing severe skin reaction. In our study, the onset of drug-related reaction was typically 2 weeks after initiating therapy. The period of increased risk was largely confined to the first 8 weeks of treatment [10]. In our study, we found that carbamazepine had a relatively protracted course, to the extent that it required longer hospitalization periods

and a more aggressive treatment regimen. Those with underlying diseases had even longer hospital stays. Bastuji-Garin et al had reported that a severity score for TEN, including factors of age, extent of total body surface, underlying disease, as well as abnormal serum urea levels (>10 mmol/L), bicarbonate (<20 mmol/L) and glucose levels (>14 mmol/L) should be considered a poor prognostic device [21]. Early administration of high dosages of steroids and additional IVIG (1 g/kg/day) were prescribed in those cases with poor responsiveness to steroid treatment in SJS/TEN. Although the use of steroids in SJS and TEN remains controversial [11-15], we have found recently that early use of the short-term IV form or oral form of prednisolone 1-2 mg/kg/day for 3-5 days, lacked any significant side effects or increase in mortality and morbidity. However, the single TEN case in our study was successfully treated with surgical debridement and supportive care with wet dressings in a burn center without administering any steroids. IVIG has been found to be able to block Fas-mediated keratinocyte death in vitro [16]. The use of IVIG in our cases of SJS was satisfactory [17]. It has been reported that SJS has been successfully treated with a combination of IVIG and steroids [18]. Early ophthalmic consultation is mandatory because ocular complications of SJS include keratoconjunctivitis sicca, symblepharon, punctual stenosis, trichiasis, and entropion can occur frequently [20]. In addition, occurrence of severe drug reaction has been reported, which suggests a genetic predisposition to adverse drug reactions [19].

In the future, a long-term cohort study might be necessary to clarify the difference between the etiologies and disease courses of these childhood mucocutaneous diseases.

References

1. Shin HT, Chang MW. Drug eruptions in children. *Curr Probl Pediatr* 2001;31:207-34.
2. Paquet P, Pierard GE. Erythema multiforme and toxic epidermal necrolysis: a comparative study. *Am J Dermatopathol* 1997; 19:127-32.
3. Leaute-Labreze C, Lamireau T, Chawki D, Maleville J, Taieb A. Diagnosis, classification, and management of erythema multiforme and Stevens-Johnson syndrome. *Arch Dis Child* 2000;83:347-52.
4. Stewart MG, Duncan NO 3rd, Franklin DJ, Friedman EM, Sulek M. Head and neck manifestations of erythema multiforme in children. *Otolaryngol Head Neck Surg* 1994;111:236-42.
5. Roujeau JC, Stern RS. Severe cutaneous adverse reaction to drugs. *N Engl J Med* 1994;331:1272-85.
6. Revuz J, Penso D, Roujeau JC, Guillaume JC, Payne CR, Wechsler J, et al. Toxic epidermal necrolysis: clinical findings and prognosis factors in 87 patients. *Arch Dermatol* 1987;123:1160-5.
7. Roujeau JC, Huynh TN, Bracq C, Guillaume JC, Revuz J, Touraine R. Genetic susceptibility to toxic epidermal necrolysis. *Arch Dermatol* 1987;123:1171-3.
8. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993;129:92-6.
9. Schofield JK, Tatnall FM, Leigh IM. Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993;128:542-5.
10. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. *Lancet* 1999;353:2190-4.
11. Kakourou T, Klontza D, Soteropoulou F, Kattamis C. Corticosteroid treatment of erythema multiforme major (Stevens-Johnson syndrome) in children. *Eur J Pediatr* 1997;156:90-3.
12. Pasricha JS, Khaitan BK, Shantharaman R, Mital A, Girdhar M. Toxic epidermal necrolysis. *Int J Dermatol* 1996;35:523-7.
13. Cheriyan S, Patterson R, Greenberger PA, Grammer LC, Latall J. The outcome of Stevens-Johnson syndrome treated with corticosteroids. *Allergy Proc* 1995;16:151-5.
14. Halebian PH, Corder VJ, Madden MR, Finklestein JL, Shires GT. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. *Ann Surg* 1986;204:503-12.
15. Roujeau JC. Drug-induced toxic epidermal necrolysis II. Current aspects. *Clin Dermatol* 1993;11:493-500.
16. Viard I, Wehrli P, Bullani R, Schneider P, Holler N, Salomon D. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 1998;282:490-3.
17. Prins C, Vittorio C, Padilla RS, Hunziker T, Itin P, Forster J. Effect of high-dose intravenous immunoglobulin therapy in Stevens-Johnson syndrome: a retrospective, multicenter study. *Dermatology* 2003;207:96-9.
18. Straussberg R, Harel L, Ben-Amitai D, Cohen D, Amir J. Carbamazepine-induced Stevens-Johnson syndrome treated with IV steroids and IVIG. *Pediatr Neurol* 2000;22:231-3.
19. Johnson-Reagan L, Bahna SL. Severe drug rashes in three siblings simultaneously. *Allergy* 2003;58:445-7.
20. Lehman SS. Long-term ocular complication of Stevens-Johnson syndrome. *Clin Pediatr (Phila)* 1999;38:425-7.
21. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: A severity of illness scores for toxic epidermal necrolysis. *J Invest Dermatol* 2000;115: 149-53.