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Erythema Multiforme, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Children

A Review of 10 Years' Experience

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Abstract

Objective: To review 10 years' experience in a tertiary care paediatric hospital of erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In addition, to apply a recently described classification system for EM, SJS and TEN in children.
Design: Retrospective study of all children with a discharge diagnosis of EM, SJS or TEN over a 10-year period.
Setting: A university tertiary care paediatric hospital.
Patients: Sixty-one paediatric patients with a discharge diagnosis of EM, SJS or TEN.
Main Outcome Measures: Epidemiology, laboratory features, causative factors, treatment methods, complications and mortality of EM, SJS and TEN in this group of patients. Comparison of correlation with aetiology of old and new classification systems in a paediatric population.
Results: Mucous membrane involvement was documented in 61% of patients. Ocular involvement was seen in 39%. Complications occurred in 21% cases, all of whom had SJS or TEN. Only one patient died as a result of their skin condition. Corticosteroids were used in 18% of cases; 95% of whom had a discharge diagnosis of SJS or TEN. The drugs most commonly identified as aetiological agents were sulphonamides and penicillins (26% each). The most frequently implicated infectious agent was herpes simplex virus (19.7%).
Classification of study cases according to Bastuji-Garin et al. indicates a strong trend toward bullous EM cases being attributable to infection and SJS/TEN cases to drugs. There was no such clear trend with respect to aetiology when diagnosis was done without the classification system.
Conclusion: EM, SJS and TEN rarely cause mortality but significant morbidity is seen. Infectious agents, particularly herpes simplex virus, and drugs, especially the sulphonamides and penicillins, are the most common aetiological agents. The classification system proposed by Bastuji-Garin et al. correlates better with aetiology than the practice that preceded it.

Background

Erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are mucocutaneous diseases associated with significant morbidity and mortality. The annual incidence of EM is unknown and has been estimated at between 0.01 and 1%.[1] The incidences of SJS and TEN are better characterised, and have been estimated at 0.4 to 1.2 and 1.2 to 6 per million person years, respectively.[2] Mortality from EM does not exist but may occur in up to 5% of cases of SJS, while 30% of cases of TEN may be fatal.[2-4] Non-fatal sequelae of these disorders are most commonly related to ocular complications.[4,5]

The causative factors of these disorders that have been identified and include infectious agents and drugs. Herpes simplex and mycoplasma pneumonia are the most common infectious agents and have been casually associated with EM and SJS.[1,6-8] All three of the disorders have been linked to drugs, with TEN being exclusively attributed to this factor.[1,3,9,10] More than 100 drugs have been associated with EM, SJS and TEN, with sulphonamides, hydantoins, nonsteroidal anti-inflammatory drugs and penicillins being the most commonly implicated agents.[3,9,11]

The entity presently called EM was first recognised in the early part of the 19th century and was known by a variety of names. The actual term 'erythema multiforme' was originated by von Hebra.[12] He described an acute mild, self-limited skin disease characterised by evolving skin lesions located primarily on the extremities, and by a tendency for recurrent episodes to occur. von Hebra originally called this presentation 'erythema exudative multiforme' (EEM). The major type presents with erosions of mucous membranes, i.e. EEM majus. In 1922 Stevens and Johnson[13] described two boys who presented with skin eruptions similar to EM associated with fever, stomatitis, and conjunctivitis. Both of the patients survived but were left with permanent visual impairment. These authors believed they had discovered a new clinical entity, most likely infectious in origin, and the condition became widely known by the eponym 'Stevens-Johnson syndrome'. In 1956 Lyell[14] described a condition in which the epidermis is damaged over a large, confluent areas of the skin surface leaving it with a scalded appearance. This condition was called 'toxic epidermal necrolysis' or Lyell's syndrome.

The similarities and overlaps between EM, SJS and TEN have led to a confusion and controversy over the precise classification and aetiology of this type of skin disorder. Lack of clear diagnostic criteria has caused the term EM to be widely used to characterise a large variety of cutaneous eruptions, with and without mucosal involvement, and even cases with mucosal inflammation without skin lesions.[15] Thomas[16] proposed classifying EM into 'minor' and 'major' subtypes. EM minor is used to describe the classic mild cutaneous eruption originally described by von Hebra, while EM major describes the more severe mucocutaneous illness. The term Stevens-Johnson syndrome has been widely accepted as a synonym for EM major or 'bullous EM'.[1,2] Because severe cases of SJS can present with extensive areas of epidermal necrolysis, TEN and SJS have been considered by some to be variants of the same process. Finally, some have seen EM, SJS and TEN as part of a continuous spectrum representing increasingly severe manifestations of a single disease entity.[1]

Paquet and Pierard,[17] using standard histology and histochemistry presented evidence that the inflammatory infiltrates of EM and TEN are strikingly different, with the former having high density T lymphocyte infiltrates and the latter cell-poor infiltrate with macrophages and dendrocytes. Recently investigators have attempted to clarify the classifications of this type of skin disorder with a consensus classification system of severe bullous EM ('EM majus'), SJS and TEN based on the pattern of EM-like lesions and the extent of epidermal detachment.[18] They have proposed five categories based purely on descriptive criteria, and have noted that bullous EM is a distinct entity usually caused by herpes virus infection which never evolves into widespread skin detachment, while SJS and TEN and the SJS/TEN overlap group are usually drug induced with cases evolving from one

category to another within this group. However, because the system is based solely on descriptive criteria, bullous EM is defined regardless of the existing evidence of herpes infection. A recent retrospective analysis has supported this classification system in a primarily adult population.[19]

Treatment for EM, SJS, and TEN consisted of primarily of removal of the offending agent treating the causative infection and adequate supportive care. Patients with significant skin detachment require treatment in an intensive care or burn unit. Some enthusiasm has existed in the past for the use of corticosteroids[20,21] but more current reviews recommend against their use.[2] Recently, the inhibition of TEN by blockade of CD95 with human intravenous immunoglobulin has been described.[22]

The purpose of this study was to review the experience of a tertiary care paediatric hospital over a 10-year period with bullous EM, SJS and TEN. Specifically, to examine the epidemiology, laboratory features, causative factors, treatment, morbidity and mortality of these diseases. Finally, we have attempted to apply the new classification system for bullous EM, SJS and TEN to these patients and compared it with the diagnoses defined without classification method in order to make a preliminary assessment of its validity in a paediatric population.

Patients and Methods

We undertook a retrospective analysis of cases of SJS, bullous EM and TEN at the Hospital for Sick Children in Toronto (HSC) between the years 1985 and 1995. The charts of all patients with an admitting or discharge diagnosis of SJS, bullous EM and TEN during this period were reviewed.

Sixty-one patients were identified where a diagnosis of SJS, EM and TEN was made by the attending dermatologist and the following data collected: demographic information (age, sex) relevant past medical history, antecedent use of medications, description and distribution of cutaneous lesions, presence and extent of mucous membrane involvement, presence of ocular involvement, physical findings other than mucocutaneous, pertinent laboratory data (complete blood count [CBC], erythrocyte sedimentation rate [ESR]), infectious disease data (cultures, cold agglutinins, viral titres), use of corticosteroids, complications and mortality.

Patients were classified as being bullous EM, SJS, or TEN based on the final discharge diagnosis noted in the chart. No criteria were used by the clinicians making the different diagnoses over these 10 years. They were separately categorised by a new classification system for bullous EM proposed by Bastuji-Garin et al.[18] The categories and definitions of this system are outlined in table I. All charts were reviewed and in detail for descrip-

Table I. Categories and definitions from the classification system for bullous erythema multiforme proposed by Bastuji-Garin et al.[18]

Categories	Bullous erythema multiforme (EM): skin detachment <10% of the body surface area (BSA), plus localised 'typical targets' or 'raised atypical targets'
	Stevens-Johnson syndrome: skin detachment <10% of the BSA, plus widespread macules (erythematous or purpuric) or flat atypical targets
	Overlap Stevens-Johnson syndrome and toxic epidermal necrolysis: skin detachment between 10 and 30% of the BSA plus widespread macules (erythematous and purpuric) or flat atypical targets
	Toxic epidermal necrolysis with spots: spots may occur with out without blisters, skin detachment above 30% of the BSA plus widespread purpuric macules or flat atypical targets
	Toxic epidermal necrolysis without spots: skin detachment >10% of the BSA with large epidermal sheets and without any macule or target
Definitions	Typical targets were defined as individual lesions <3cm in diameter with a regular round shape, well defined border, and at least three different zones, i.e. two concentric rings around a central disk. One ring consisted of palpable oedema, paler than the central disk
	Raised atypical targets were defined as round, oedematous, palpable lesions reminiscent of EM but with only two zones and a poorly defined border
	Flat atypical targets were defined as round lesions reminiscent of EM but with only two zones and/or a poorly defined border, non-palpable with the exception of a potential central blister
	Macules with or without blisters were defined as non-palpable, erythematous, or purpuric lesions with irregular size and shape, often confluent Blisters often occurred on all or part of the macule

tions of the cutaneous manifestations of the disease. Whenever available the dermatology consultation was used as the primary source for a description of the lesions. If this was not available then the observations of the most senior paediatric staff or house staff was utilised. Patients were then placed into one of five groups of the new classification system as outlined in table II. Those patients that did not fit the criteria for any of the five categories were considered unclassified.

Individual cases were considered to be drug related if the patient was exposed to the agent within several 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 one week prior to the onset of the rash. Cases were considered to be definitely herpes simplex virus-related only if herpetiform lesions were documented. Cases were considered to be definitely mycoplasma related only if mycoplasma titres and/or cold agglutinins were available.

The number of cases attributable to drugs, infectious agents, both or neither were tabulated and analysed by specific agent. Diagnostic category using the standard definitions for bullous EM, SJS and TEN were compared with the category obtained using the new classification system. Diagnosis according to aetiology was tabulated for both systems of classification and compared.

Results

Of the approximately 300 000 children admitted to HSC between 1985 and 1995, 61 patients were discharged with a diagnosis of EM, SJS or TEN. The mean age was 4.8 years. Thirty-seven patients (60.6%) were males, and 24 (39.3%) were female. ESR was available for 29 patients (48%). The mean ESR was 43.4 ± 27.2 mm/h, with a range from 22 to 137 mm/h. A CBC was available for 53 patients (87%). The mean WBC was 11.125 ± 5.24 $\times 10^9$/L, with a range from 0.7 to 25 $\times 10^9$/L.

Thirty-seven patients (61%) had mucous membrane involvement. Oral, genital and anal lesions were those predominantly observed. Oral lesions occurred in 95% of cases that had mucous membrane involvement. Oral lesions ranged from isolated vesicles or bullae to involvement of the entire buccal mucosa, pharynx, tongue and lips. Anogenital lesions were documented in 50% of the patients with mucous membrane involvement, and were most commonly described as vesiculobullous or ulcerative. Other mucosal surfaces which were infrequently involved included: oesophagus, colon, nasal cavity and pulmonary.

Ocular involvement occurred in 24 patients (39.3%). Haemorrhagic conjunctivitis, corneal ulceration, conjunctivitis with purulent discharge, scleritis, blepharitis and photophobia were documented. Complications included: corneal ulcerations, pseudomembrane formation and adhesions. Complications occurred in 13 patients (21.3%), and were seen only in patients with SJS or TEN. Complications included: pigmentation changes (hyperpigmentation or hypopigmentation), sepsis, altered pulmonary function, urinary retention, severe hepatitis, phimosis and ocular complications. Only one child (1.6%) died as a result of their condition. This was a 3-month-old baby boy with a diagnosis of SJS secondary to the use of diazoxide. The child died 5 days after admission due to multiorgan failure and sepsis.

Eleven of the 61 cases were treated with corticosteroids (18.0%). All but one of the patients treated with corticosteroids had a discharge diag-

Table II. Classification of severe bullous erythema multiforme (EM) according to Bastuji-Garin et al.[18]

	Bullous EM	SJS	Overlap SJS/TEN	TEN with spots	TEN without spots
Detachment	<10%	<10%	10-30%	>30%	>10%
Typical targets	Yes				
Atypical targets	Raised	Flat	Flat	Flat	
Spots		Yes	Yes	Yes	

SJS = Stevens-Johnson syndrome; **TEN** = toxic epidermal necrolysis.

nosis of SJS or TEN. Both intravenous and oral corticosteroids were used. The aetiology of the mucocutaneous disorder was attributed to drugs alone in 33 cases and to infection only in 16 cases. Both drug and infectious agents were identified in ten cases, and neither a drug nor infectious agent was identified in two cases (table III). The infectious agent most commonly implicated was herpes simplex virus, identified in 12 cases (19.7%). Other infectious agents are delineated in table IV. The 61 cases were divided by the discharge diagnosis as follows: EM – 30 patients, SJS – 28 patients, TEN – three patients. When the cases were classified according to the system of Bastuji-Garin et al.[18] they were divided as follows: bullous EM – 23 patients, SJS – 23 patients, SJS/TEN – three patients, TEN with spots – five patients, TEN without spots – three patients, unclassified – four patients.

When the standard classification system was compared with the new system it was found that all cases that were called EM according to the old system and were classifiable according to the new system fitted into the categories of bullous EM or SJS. Those cases that were classified as SJS by the standard system split among all five categories of the new system. The three cases that were called TEN by the standard classification all fit into the category TEN with spots using the new system. The results of the comparison of the two systems of classification are summarised in table V.

The original diagnosis (with no apparent system) was compared with the new system with no regard to diagnostic classification as related to identified aetiology. Using the standard system there was significant variation within the EM and SJS groups as to aetiology. Drugs were identified in 13 of the 30 cases diagnosed as EM, infectious agents in nine cases and both agents identified in two. Of the 28 cases identified as SJS, 17 were attributed to drugs, seven ascribed to infection and two attributable to both. All cases of TEN were attributable to drugs. Using the new classification there was less variation as to aetiology. Nineteen of the 23 cases classified as bullous EM were attributable to infection only or infection and drugs (14 infection only and 5 both). Only four cases were attributed to drugs only or to neither infection nor drugs. In the SJS group 21 of the 23 cases were attributed to drugs (17 drug only and 4 both). Only one case was attributed to infection only. The 11 cases that were classified into the overlap SJS/TEN, TEN with spots and TEN without spots were all attributed to drugs only. The results of the diagnostic classification with respect to aetiology are summarised in table VI.

Table III. Drugs associated with erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (n = 61)

Drug	Number of cases (%)
Sulphonamides	16 (26.2)
Penicillins	16 (26.2)
Cephalosporins	8 (13.1)
Erythromycin	4 (6.5)
Phenobarbital (phenobarbitone)	2 (3.3)
Carbamazepine	2 (3.3)
Diazoxide	1 (1.6)
DPTP	1 (1.6)

DPTP = diphtheria-pertussis-tetanus-polio vaccine.

Table IV. Infectious association erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (n = 61)

	Number of cases (%)
Herpes simplex virus	16 (26.2)
Viral urinary tract infection	4 (6.5)
Mycoplasma pneumonia	3 (4.9)
Epstein-Barr virus	2 (3.3)
Viral meningitis	1 (1.6)
Viral gastro-enteritis	1 (1.6)
Cytomegalovirus	1 (1.6)
Infected central line	1 (1.6)
Streptococcal infection	1 (1.6)

Discussion

This study has confirmed that bullous EM, SJS, and TEN requiring hospitalisation are relatively uncommon disorders. Only 61 cases requiring admission were identified over a 10-year period from over 300 000 total admissions to a large tertiary care hospital serving as a referral centre for a major metropolitan area. Presently, the published evidence does not clearly delineate differences in epi-

Table V. Comparison of Bastuji-Garin et al.[18] classification and standard classification methods in the diagnosis of a sample of paediatric patients (n = 61)

Diagnosis under standard classification	Diagnosis under Bastuji-Garin classification					
	bullous EM	SJS	overlap SJS/TEN	TEN with spots	TEN without spots	unable to classify
EM (n = 31)	15	14	0	0	0	2
SJS (n = 27)	9	8	3	2	3	2
TEN (n = 3)	0	0	0	3	0	0
Total	**24**	**22**	**3**	**5**	**3**	**4**

EM = erythema multiforme; **SJS** = Stevens-Johnson syndrome; **TEN** = toxic epidermal necrolysis.

demiology, aetiology and prognosis of severe skin reactions in children, as compared with adults. Mortality for the group of patients identified was low, with only one of the 61 total cases being fatal. As has been previously reported, mortality in bullous EM is rare and there were no deaths in the 30 patients with this diagnosis.[4] A mortality rate of up to 5% has been reported in cases of SJS.[3] One of the 28 patients identified with this syndrome in our series died, leading to a mortality rate of 3.6%. The significant mortality of up to 40% reported in TEN[5] was not seen, as none of the patients with TEN patients; however, only three patients with this diagnosis were identified in the series.

Sulphonamides and penicillins have been previously reported to be commonly implicated as aetiological agents in bullous EM, SJS and TEN,[1] and these were the most commonly reported drugs in our series. Previous reports have not identified a significant role for the cephalosporins as causative agents in the group of diseases. In the study, however, they were the third most common pharmacological agent identified (8 cases; 13%). The increased incidence seen may be due to changing prescribing practices, as newly available second and third generation oral cephalosporins have come into widespread clinical use. Alternatively, this may reflect a unique sensitivity in the paediatric age group.

The infectious agent most commonly linked to SJS and TEN in our series was herpes simplex virus, where 16 of the cases (26.2%) were associated with herpes infection. Mycoplasma pneumonia has also been causally related to these diseases and we observed three such cases. No other specific infectious aetiology was associated with a significant number of cases.

It is of note that in ten cases both drugs and infectious agents were identified as possible precipitants to the disease. This made analysis of the

Table VI. Diagnostic classification as related to aetiology for standard and new (Bastuji-Garin et al.[18]) classifications (n = 61)

	Drug only	Infectious only	Both	Neither
Diagnosis under standard classification				
EM	13	9	6	2
SJS	17	7	4	0
TEN	3	0	0	0
Diagnosis under Bastuji-Garin classification				
Bullous EM	3	14	5	1
SJS	17	1	4	1
SJS/TEN overlap	3	0	0	0
TEN with spots	5	0	0	0
TEN without spots	3	0	0	0
Unclassified	2	1	1	0

EM = erythema multiforme; **SJS** = Stevens-Johnson syndrome; **TEN** = toxic epidermal necrolysis.

data more difficult, as cases could not always be ascribed to a single aetiological agent. Because it is such common practice for antibacterials to be prescribed to children, this problem is likely to confound any analysis of aetiology in the paediatric population. It is biologically plausible that an interaction between an infectious agent and a drug, or its metabolite, may precipitate severe skin reactions.

The lack of clear diagnostic criteria for bullous EM, SJS and TEN has created confusion in the classification of these illnesses.[11] Furthermore, determination of aetiology has been made difficult by lack of universal agreement as to whether these are distinct diseases or rather all part of the 'EM spectrum'. The difficulty in ascribing aetiology based on the standard classification of EM/SJS/TEN is clear from the data in table VI. Drugs are the most common factor seen for both bullous EM and SJS; however, both have significant numbers of cases attributed to infection. Only the cases of TEN can all be attributed to a single aetiology – drugs.

While the cases are classified according to the system of Bastuji-Garin et al.[18] there is a clearer relationship between diagnostic category and aetiology (table VI). While there is still not a perfect correlation between the two, there does exist a strong trend toward the bullous EM cases being attributed to infection and other four categories being associated with drugs. Of the 34 non-bullous EM cases, drugs were associated either alone or together with infection in 32. The authors have proposed that bullous EM group is associated with herpes simplex virus infection and the other categories attributable to drugs. It is of note that of the 15 patients with a diagnosis of herpes simplex virus infection, 13 were classified into the bullous EM group and both of the remaining two that were classified as SJS had also been exposed to drugs. We conclude that the new system of classification of bullous EM/SJS/TEN as proposed by Bastuji-Garin et al.[18] appears to be an improvement over the previous system and that the diagnostic groups appear to correlate well with aetiology in a paediatric population.

Limitations of this study are largely associated with its retrospective design. Identification of aetiological factors may not have been complete for all patients. The division of cases was based on discharge diagnosis; however, in some cases there was a lack of agreement among the clinicians as to what the diagnosis was. The classification of cases into the system proposed by Bastuji-Garin et al.[18] was based on descriptions of the patient's cutaneous lesions as documented in the chart and not on photographs of the patients. It is possible that some of the cases were misclassified. In addition, the review of cases was not done by a review committee blinded for possible causes of the disease. A prospective study with a standardised data collection set as well as photographs of the patients could eliminate these problems. Due to the low incidence of these diseases such a study would benefit from being multicentre in design.

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