Diagnosis and Management of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Introduction

Stevens-Johnson Syndrome(SJS) and Toxic Epidermal Necrolysis (TEN) are variants of a spectrum of conditions characterised by erythematous macules evolving to epidermal detachment and mucous membrane erosions. In SJS there is less than 10% body surface area involvement, in TEN more than 30% and 10-30% overlap cases.

It is important to be able to recognise Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and manage them properly. The mortality rate of SJS and TEN is high: even in moderately severe cases it could be up to 30%. For those who survive, there could be troublesome late complications. Moreover, since the use of drug is the most important cause, the identification and removal of the causative medication is of paramount importance to halt the progression of the conditions and to prevent recurrence from inadvertent re-challenge.

Recognising SJS and TEN

We could recognise SJS and TEN early if we are familiar with their clinical features, especially those earlier ones. Many patients with SJS and TEN begin with the prodromal symptoms of fever, headache and myalgia. The SJS and TEN skin eruptions1 first appear as erythematous then dusky or purpuric macules. The lesions are usually irregularly shaped, discrete in the beginning then coalesce with one another. Atypical target lesions could be seen but they are not the three-zone target lesions seen in erythema multiforme. The rash first appears on the face and upper part of the trunk and proximal part of the extremities and spread rapidly to the rest of the body. Lesions soon developed into flaccid blisters. For those non-blistered rash, Nikolsky sign (separation of epidermis from dermis with lateral pressure) can be demonstrated, which is an important though not pathognomonic sign. Finally the necrotic epidermis comes off leaving large areas of red exudative dermis exposed.

The mucous membrane is always involved in SJS and TEN, commonly precede the rash but sometimes after. Erythema is followed by painful erosions on the buccal, ocular and genital mucosae, and usually more then one site are involved. More than 80% of patients have conjunctival involvement, sometimes leads to corneal ulceration, anterior uveitis and synechiae. Ocular involvement in SJS and TEN could result in the most debilitating late complications.

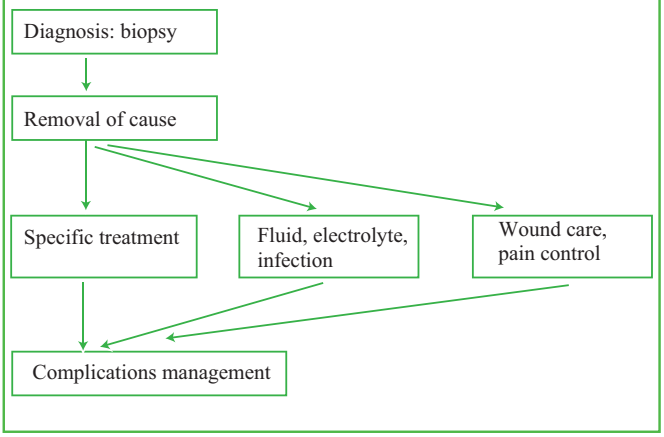
SJS and TEN do not limit themselves to the skin. Pulmonary and digestive system involvements are not uncommon. A quarter of patients have shortness of breath, hypoxia and haemoptysis, and the degree of pulmonary involvement is not necessary in proportion to the degree of skin involvement. Chest X-ray could show features of interstitial involvement but differentiation from infection is important, which could be helped with fibreoptic bronchoscopy. Gastrointestinal tract involvement will result in diarrhoea, malena and oesophageal necrosis. Renal involvement will result in proteinuria, haematuria and azotaemia.

The prodrome of fever, myalgia, headache; the appearance of dusky rash on the face and proximal limb; mucosal erosion, and the positive history of drug exposure should alert the physician to the possibility of SJS and TEN

Managing Patients with SJS and TEN

SJS and TEN are life threatening conditions that need intensive care with experienced physicians and specialis nurses and multidisciplinary team work. The framework of the management is depicted in Chart 1.

Chart 1 Management of SJS/TEN



Diagnosis

All suspected cases of SJS and TEN should be confirmed by skin biopsy for histologic and immunofluorescence examinations. Early lesion shows suprabasal layer apoptotic keratinocytes. Later lesion shows full-thickness epidermal necrosis and separation of epidermis from dermis. A number of important

conditions mimic SJS and TEN (Table 1) hence a histological evidence is important. Since 90% SJS and TEN has mucous membrane involvement the absence of such should prompt one to consider alternative diagnosis.

Table 1 Mimickers of SJS and TEN

Erythema multiforme major
Staphylococcal scalded skin syndrome
Purpura fulminant
Disseminated intravascular coagulation with skin necrosis
Acute generalised exanthematous pustulosis
Generalised bullous fixed drug eruption
Chemical toxicity (methotrexate, colchicines etc)
Burns
Graft-versus-host disease
Pemphigus

Erythema multiforme (EM) could easily be mixed with SJS since both present with rash and oral mucosal erosion. The classification by Bastuji-Garin[2] separated erythema multiforme from SJS/TEN although it is not universally agreed. EM is different from SJS and TEN in many ways (Table 2). Infection is the major cause of EM and the commonest implicated infections are Herpes simplex and Mycoplasma pneumoniae although some other infectious agents have been reported, whereas drug is considered as an uncommon cause. The typical target lesions in EM have three concentric zones: central dusky disk, middle pale ring, outermost erythematous halo and they are not found in SJS and TEN. Characteristically all lesions of EM are papular and in acral distribution at least initially whereas in SJS and TEN rash start on face and proximal limbs. Although in EM there could also be mucosal involvement they are mostly limited to oral mucosa.

Table 2 Comparing EM and SJS/TEN

EM	SJS/TEN
Infection: Herpes simplex, Mycoplasma pneumoniae	Drug causes
Papular erythematous lesions	Macular dusky lesions
Typical targets with three zones	Target lesions atypical
Aral distribution initially	Face and proximal limb initially
70-% mucosal involvement but limited to oral mucosa usually	90% mucosal involvement and many on more than one sites
Fever and constitutional symptoms absent	Fever, headache, myalgia common
Most <10% body surface area	Extensive with epidermal necrolysis
Mild course, recovers in 1-4 weeks	High mortality in severe cases
Recurrence common and many are herpes simplex related	Recurrence uncommon unless causative drugs re-challenged

Staphylococcal scalded skin syndrome (SSSS) presents initially as a macular exanthema which might quickly evolve to blistering eruption with positive Nikolsky's sign and mimic SJS and TEN. SSSS more commonly occurs in infants or adults with renal failure. A Tzanck smear will find acantholytic cells in SSSS but not TEN. Skin biopsy with frozen section examination will find intradermal cleavage with acantholysis in the subgranular layer whereas in SJS and TEN full-thickness epidermal necrosis and dermal-epidermal separation are found. The diagnosis of SSSS instead of SJS/TEN will enable the early use of antibiotics against Staphylococcus.

Removal of Cause

In 70% of SJS and TEN drug cause could be identified and more than 100 agents have been reported3. Drug history taken carefully and repeatedly, involving family members, enquiring family doctors, and taking over-the-counter non-prescription items into consideration are necessary before the causative agent can be identified. Since many patients could be taking several agents at the same time, the true causative agent could be hard to isolate. The temporal relationship between the intake of the agent and onset of condition is an important factor. SJS and TEN usually begins less than 8 weeks but more than 4 days from the first intake of the agent. Look for drugs that were added within this period. Only re-challenged drugs will elicit the condition in a few hours. Some medications have higher risk of causing SJS and TEN whereas in some other medications SJS and TEN has not been reported (Table 3). Infection is not a common cause of SJS and TEN although there have been case reports of Mycoplasma pneumonia. The identified culprit should be removed immediately and labelled "allergic" so that it would not be re-challenged inadvertently. In case of complicated drug history and a definite single causative agent could not be identified, only the necessary medications should be retained.

Table 3 Drugs and SJS/TEN

High Risk	No reports of SJS/TEN
Allopurinol	Angiotensin-converting enzyme inhibitors
Carbamazepine	Aspirin
Lamotrigine	Aldactone
Nevirapine	Beta-blockers
NSAIDs(Oxicam)	Calcium channel inhibitors
Phenobarbital	Furosemide
Phenytoin	Sulfonylurea
Phenylbutazone	Thiazide diuretics
Sulphadiazine	
Sulfapyridine	
Sulfamethoxazole	
Sulfasalazine	

Specific Treatment

SJS and TEN are life threatening conditions. The success of treatment depends on early recognition of the condition, prompt removal of the causative medications and intensive supportive care in a well-equipped hospital.[4] Several agents with anti-inflammatory or immunosuppressive properties have been tried to alter the course of the disease but no single agent has their efficacy clearly proven by clinical trials.

1. Intravenous Immunoglobulin (IVIG)

Prepared from pooled plasma, IVIG contains immune antibodies that interfere with the apoptotic pathway mediated by the Fas ligand and receptor. Theoretically it is best to give IVIG early (within 24-72 hours from first appearance of bullae)[4,5] before Fas ligand and receptor binding has occurred, although it may still be effective if new bullae are still appearing. Sucrose-depleted IVIG is preferred since it has lower possibility of renal toxicity. Patient with IgA deficiency will develop anaphylaxis to IVIG. It is best to obtain a patient's IgA level before administering but awaiting the report might delay treatment. History of recurrent sinopulmonary infection and gastrointestinal infection may help to identify those with IgA deficiency which is very rare.

Results of studies of IVIG on SJS and TEN has been conflicting, and IVIG should not be considered as a routine treatment. Some studies have suggested the higher dose of 3g/kg total dose given over 3 days has better effects over the lower dose of 2g/kg total dose.

2. Systemic Corticosteroid
Some studies have advocated the use of systemic corticosteroids in the early stage of SJS and TEN. Other studies failed to prove the effect of the agent and have demonstrated an increase in the chance of sepsis and other complications. Balancing available evidence especially the more recent ones,[1] systemic corticosteroids cannot be recommended in TEN. Its use in SJS is still controversial but should not be recommended when extensive skin loss has already occurred.

3. Cyclosporin A
Supported by favourable outcomes[6] in several case reports and series, which used cyclosporin A at a dose of 3-4mg/kg/day in short term, thus avoiding its side effects which commonly occur in long term use, this agent seems promising but more comprehensive studies are needed.

4. Other Agents
Theoretically removal of the offending medication, its metabolites or cytokines by plasmapheresis or haemodialysis could help the improvement of SJS and TEN. However the lack of good clinical evidence and the risk of sepsis associated with in-dwelling catheter does not support these as recommendable treatments. Thalidomide[7] based on its anti-TNF effect has been tried but the study was prematurely terminated since excess mortality was reported.

Management of Fluid, Electrolyte, Respiration and Infection

In the absence of proven effective specific agent, the success in treating SJS and TEN depends very much on supportive care. Since SJS and TEN can deteriorate rapidly, intensive care unit or burn centre care is recommended. Fluid loss and electrolyte imbalance should be closely monitored and corrected. Peripheral line is more recommendable than central, which has a higher chance of infection, but good peripheral venous access is difficult to find. All lines should be checked for signs of infection daily and changed two times a week with tips of lines and catheters sent for culture. Nutrition support with nasogastric tube helps healing. Respiratory rate and oxymeter monitoring are important. Raised urea level, blood glucose above 14mm/L and neutropenia are unfavourable prognostic factors and should be monitored.

Sepsis is the main cause of death. Cultures should be taken frequently from the cutaneous erosions, mucosal erosions, blood and urine to obtain the microbiology and their sensitivity profile. Signs of infection should be monitored closely and systemic antibiotics should be promptly administered when signs of infections (fever or falling body temperature, rigour, hypotension, decrease in urinary output, respiratory failure, poor glycaemic control and impaired consciousness, etc) are detected. Prophylactic antibiotic is contraindicated since this will encourage the appearance of resistant strains.

Wound Care and Pain Control

Painstaking wound care is the backbone to management of SJS and TEN.[1,4] Good wound care reduces the chance of infection and pain. There is no standard protocol on the wound dressing. Various non-stick dressing has been used but sulfa-containing material should be avoided to prevent systemic sensitisation and leucopenia. Use air-fluidised mattresses to prevent pressure sore. The environment temperature is maintained at 28-30 degree Celsius to prevent hypothermia. Debridement of necrotic epidermis is not necessary. Adequate pain control many a time needs morphine group of analgesics. Respiratory depression should be watched out if opiates are used.

Oral mucosal ulceration is very painful. Chlorhexidine rinses help in maintaining good hygiene and white-soft paraffin on the lips relieves the pain. Complications on the eyes could result in blindness and an ophthalmologist's care is necessary. Artificial tears, antibiotics eye drops every two hourly and mechanical disruption of early synechiae is needed.

Complications

Sepsis is the most important cause of mortality. Extensive erosions put patients at risk of infection by bacteria and fungi which will result in pulmonary complications and multi-organ failure. If respiratory failure develops, ventilation support is needed.

Late ophthalmic complications are seen in up to 75% of patients, hence early treatment is needed. Hyperpigmentation and hypopigmentation are common and sometimes scars and nail dystrophy may result. Genital adhesions resulting in dyspareunia, pain and bleeding should be watched out. Gastrointestinal, bronchial, urethral and anal complications are less common. Post-traumatic stress disorder is also possible and some patients may need psychiatrist's care. All patients recovering from SJS and TEN should be followed-up for development of these complications which could be delayed but debilitating.

Prognosis

Depending on the severity, the clinical course of SJS and TEN may last up to a few weeks. It should be noted that the prognosis is not related to type or dose of the causative medication. A SCORTEN prognostic scoring system[8] has been developed to correlate mortality with selected parameters.

Prognostic factors	Points	SCORTEN	Mortality Rate
▪ Age > 40	1	0-1	3.2%
▪ Heart rate >120/min	1	2	12.1%
▪ Cancer or haematologic malignancy	1	3	35.8%
▪ >10% body surface area	1	4	58.3%
▪ Serum urea >10mm/L	1	>5	90%
▪ Serum bicarbonate<20mm/L	1		
▪ Serum glucose >14mm/L	1		

Conclusion

Successful management of SJS and TEN requires the early recognition of the conditions, diagnosis with biopsy, identification and removal of the causative drugs and intensive multidisciplinary management in a hospital with experienced medical and nursing personnel.

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