

MANAGEMENT OF STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

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ABSTRACT

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent a spectrum of the same disease caused by drugs in almost all cases. Early referral and supportive care in a specialised unit reduce mortality. The article discusses important management principles when caring for SJS/TEN patients.

DEFINITIONS

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent a spectrum of the same disease and are arbitrarily delineated by percentage body surface area (BSA) involved by skin necrosis and stripping. SJS affects < 10% BSA while TEN involves > 30% BSA. SJS/TEN overlap lies between these two. Systemic features or drug hypersensitivity may be present.

Erythema multiforme in all its guises is now considered to be a reaction post-infection rather than post-drug.

AETIOLOGY

SJS/TEN is almost always drug-related. The pathogenesis is multifactorial and is probably due to a dynamic interplay between acquired and constitutional factors in the presence of threshold amounts of the drug or its metabolites. An inability to detoxify intermediate drug metabolites which may serve as haptens when complexed with host epithelial tissue could initiate an immune reaction. Once initiated various triggers propagate the immune response leading to keratinocyte apoptosis, mainly mediated by Fas and Fas ligand and tumour necrosis factor (TNF), or a state of tolerance is induced. Propagating triggers are produced by the immune system with inflammatory episodes induced when cells are stressed.

A wide variety of causative drugs have been identified and these are related to the spectrum of local disease and local prescribing practices. Common drug causes in South Africa include antituberculosis drugs, sulphonamides, anticonvulsants and antiretrovirals (nevirapine).

RELATIONSHIP WITH HIV

Initial data at our centre show that most of the patients with SJS/TEN are HIV infected and between 2004 and 2006 the incidence ranged from 40% to 69%. Case series of SJS/TEN in the literature show a striking increase in prevalence of HIV infection.¹⁻³

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Fig. 1. Skin changes in SJS/TEN. (a) Erythematous macules with early epidermal necrosis evident as irregular purple areas; (b) erythema with epidermal necrosis, blisters and erosions; (c) stripped necrotic epidermis.

Some studies show a direct relationship between the incidence of SJS/TEN and HIV infection with HIV-infected persons more likely to develop SJS/TEN.⁴⁻⁶

CLINICAL FEATURES

SJS/TEN is a serious condition with reported mortality rates in the literature ranging between 10% and 75%.

The patient may present with a prodromal phase of fever, malaise, cough, stinging eyes and sore throat, for which the patient often consults a doctor and is treated for an upper respiratory tract infection. This is followed, 1-3 days later, by a red, measles-like rash which progresses to a dusky purple/red colour with blistering and epidermal detachment (Figs 1a -1c).

Palms and soles are often involved early with erythema, pain and blisters (Figs 2a & 2b). At least one of the mucosal surfaces is eroded. The eyes, oropharynx (Fig. 3) and genitalia are involved in > 90% of patients. The respiratory system can be extensively involved. The skin and mucosal lesions are painful. Leucopenia, eosinophilia and abnormal liver enzymes have been reported⁷ and some patients may show prerenal impairment due to reduced fluid intake in relation to their increased overall fluid needs.

The course of the disease is unpredictable and at presentation it is impossible to predict the final severity and extent of the disease; therefore it is important to monitor these patients until the evolution is complete.

PROGNOSTIC FACTORS

Seven parameters have been identified as risk factors and incorporated into a disease severity score called SCORTEN which predicts mortality.⁸ These are:



Fig. 3. Mucosal changes in SJS/TEN. Haemorrhagic eroded mucosa and peri-orofacial skin.

- Age over 40 years
- Malignancy
- Tachycardia (pulse > 120/minute)
- Initial epidermal detachment of > 10%
- Serum urea level > 10 mmol/l
- Serum glucose level > 14 mmol/l
- Bicarbonate level > 20 mmol/l

Other comorbidities can often be the cause of higher mortality rates and have an additive effect to the above-mentioned factors.

MANAGEMENT

Early diagnosis

Early diagnosis has been shown to reduce mortality rates.

Ascribing causality

A level of probability for the association between the clinical picture and the drug requires a risk evaluation of the identified drugs for causing SJS/TEN. This should incorporate an assessment of the temporal relationship between the use of the drug and the occurrence of the reaction, including responses to drug withdrawal.⁹ This is where a good history becomes important. The enquiry should include herbal medication, 'natural products', once-off medication, medication obtained from friends, etc.

Early withdrawal

Early withdrawal of the offending drug improves outcome. This is more effective for drugs with shorter half-lives but it seems to be less important for drugs with longer half-lives.¹⁰

Early transfer

Early transfer to and management in a specialised unit improves outcome. This improvement has been attributed to proper nutrition, avoidance of antibiotics and corticosteroids, and implementation of clearly defined wound management procedures.¹¹

Good nursing and supportive care

This is the mainstay of treatment for these patients and specific therapies play less of a role in the overall management.



2a



2b

Fig. 2. Palmoplantar changes in SJS/TEN. (a) Painful erythema with early epidermal necrosis (purple areas) of the sole; (b) painful necrotic soles with secondary blistering. Similar changes occur on the palms.

Multidisciplinary approach

SJS/TEN is a systemic disorder and it can involve many organs. For this reason, a team approach which includes dermatologists, burns unit specialists, ICU specialists, nutritionists, ophthalmologists, microbiologists, infectious disease specialists, general physicians and a pain management team centered around a good core of experienced nurses assures optimal management.

Adequate nutrition

Nutrition is an integral part of management as SJS/TEN is a hypermetabolic state and there are increased energy and protein dietary requirements which are proportional to the BSA affected.

Oral intake is often difficult because of upper gastrointestinal tract (GIT) injury; therefore diet and fluid modification are important. Early in the disease when the dysphagia and odynophagia are severe, a fluid diet is preferable and more tolerable for the patient. Factors to consider with regard to oral feeds are temperature, acidity (hot, cold and acidic food and beverages worsen pain), texture and moisture of food as smooth, moist food is more tolerable than rough, abrasive food.

If nutritional requirements exceed the ability to eat then there is a role for enteral feeding,¹¹ but it is important to encourage oral feeds to avoid adhesions in the upper GIT.

Glycaemic control can be a problem as a result of stress and previous treatment with systemic steroids. As hyperglycaemia is one of the risk factors for poor outcome, close control of blood glucose should be maintained.

Skin care

Careful protection of the exposed dermis and early re-epithelialising skin is paramount to prevent further detachment. Unbroken epidermis, even if dead, serves as protection for underlying viable and regenerating tissue. Daily baths (Fig. 4) and the use of clean, sterile, non-adhesive dressings (Fig. 5) as required are routine. It is important to observe the skin closely during bathing, noting infected areas from which swabs should be taken. These are important for early empirical antibiotic therapy if the wounds become septic while blood cultures are outstanding.

Pain management

Pain control is an integral part of the management of SJS/TEN but there is not much literature available to guide one except for burn pain management. SJS/TEN patients experience background pain which is present at rest and is of low intensity. During procedures the pain is more intense and short-lived and the latter is referred to as procedural pain. Management of pain has to cater for both types. It has been shown that burn patients tend to be undertreated for pain and it would not be presumptuous to assume the same for SJS/TEN.

Pain management has to be individualised, taking into consideration the clinical needs of the patient, viable route of administration, risk of respiratory suppression and monitoring facilities. In a non-ICU setting full consciousness is preferable as is oral therapy for reasons already mentioned. Oral transmucosal, short-acting, medium-potency opioids are best for procedural pain. Anxiolytics such as low-dose benzodiazepines can be added and these are more effective for patients with high pre-procedure anxiety and high baseline pain



Fig. 4. Care of the skin in SJS/TEN. Daily baths.



Fig. 5. Care of the skin in SJS/TEN. Non-adherent, sterile dressings.

scores. Longer-acting, mild- to moderate-potency opioids together with paracetamol should be given for background pain.¹²

Monitoring

Frequent monitoring of vital signs is a vital part of management as they offer the first signs of a worsening systemic condition. The earliest signs of sepsis are hypothermia, tachycardia, hypotension, confusion and diarrhoea. These require prompt intervention.

Role of surgical debridement

This is not recommended in most centres.

Temperature control

With the loss of the integument patients with SJS/TEN have impaired temperature control and are best nursed in rooms with ambient temperature and humidity.

Fluid balance

Careful monitoring of fluid balance with strict input and output charts is essential because the patients have significant insensible fluid loss and often present with dehydration and renal impairment. This needs to be aggressively corrected as it is one of the risk factors for a poor outcome.

Role of prophylactic antibiotics

Most clinicians agree that these are best left for proven infections. Careful monitoring for any signs of infection is critical to facilitate prompt sepsis intervention.

Intravenous lines

These can be a source of sepsis in patients with stripped skin. If the patient is taking sufficient oral fluids then they are not indicated. Specific indications include a confirmed infection needing parenteral antibiotics or resuscitation.

Eye care

The most common problem is conjunctival involvement. This can be mild but may be severe leading to scarring and its complications which include blinding keratopathy and limbal stem cell deficiency.

General supportive care with 1-2-hourly lubrication and early assessment by an ophthalmologist to prevent or manage these complications is indicated. There is a role for contact lens use to prevent synechiae or blunt-instrument release of developing synechiae. Bandage contact lenses for non-healing corneal ulcers and amniotic membrane transplantation for severe persistent corneal damage may be necessary.¹³ Up to 79% of patients with eye involvement in the acute stage of SJS/TEN have long-term eye problems such as xerophthalmia, ectropion, entropion, symblepharon, corneal opacity and pannus formation.^{14,15} Management should aim to keep these disabilities to a minimum.

Genital care

Good hygiene and the use of non-adhesive dressings are usually adequate to allow healing of mucosal erosions. Every effort should be made to prevent adhesions in areas where two eroded surfaces are opposed. This is especially important in uncircumcised men as phimosis may complicate management.

Indwelling urinary catheters should be avoided, if possible, as they can be a source of sepsis in patients with little skin-barrier protection. They may be essential however if nursing care is compromised by constant soiling.

Upper GIT care

Continuous and frequent oral intake should be encouraged as this helps to maintain a patent system and prevent adhesions. Mild, medicated mouthwash should be used 2-hourly to clean the mouth. A lubricating cream can be used to soften haemorrhagic lip crusts prior to removal. Paraffin gauze dressings and lubricating cream are used to cover erosions and avoid fissuring. An antifungal therapy should be used if oral thrush develops. Lip and mouth lesions tend to persist after other areas have re-epithelialised.

Respiratory system (RS)

Some authors report RS involvement to be common, with 10-20% needing artificial ventilation.¹⁶ In our experience RS involvement is usually mild and very few patients ever need ventilatory support. They can present with tracheobronchial mucosal necrosis, pulmonary oedema, adult respiratory distress syndrome and infectious pneumonia or pneumonitis. Pooling of saliva and secretions may predispose to aspiration and therefore these need to be cleared frequently. Coughing may be difficult, posing a further risk of RS infection.

Specific management

Systemic steroids

There is controversy regarding use of systemic steroids^{7,13} but evidence suggests that at most they are not beneficial and at worst can be harmful to the patient if used in large doses. For patients in septic shock, treatment with low doses of hydrocortisone may have better outcome but this has not yet been shown in those with associated SJS/TEN.¹⁷

Intravenous immunoglobulin (IVIG)

IVIG blocks Fas/Fas ligand interaction, preventing progression of keratinocyte apoptosis.⁷ If used early in SJS/TEN it may halt progression of the disease. French¹⁸ reviewed 9 prospective and retrospective uncontrolled studies, containing more than 10 patients each, in which patients with SJS/TEN were treated with IVIG. He concluded that at doses of > 2 mg/kg it is safe and decreases mortality rates. Mittman *et al.*^{19,20} came to the same conclusion. As one cannot predict prognosis in SJS/TEN its true benefit on mortality is not clear. The cost to benefit ratio is the main factor that restricts its use outside of developed countries.

Cyclosporine

Chave *et al.*⁷ reviewed 10 papers which included a total of 20 patients treated with cyclosporine. They concluded that, if given early in the disease, at 3-5 mg/kg daily, either intravenously or orally, over 2 weeks, it arrested progression of disease without any increased risk of sepsis.

Plasmapheresis and haemodialysis

These have been advocated by some authors to remove drug metabolites and responsible cytokines from circulation^{7,21} but both are of questionable value.^{15,22}

MedicAlert

It is a critical and often neglected part of the management of these patients to prevent a recurrence of this potentially life-threatening condition. It is the responsibility of the attending doctor to at least facilitate this process.

Rechallenging

Most authors recommend that SJS/TEN patients should never be rechallenged. There is a strong association between SJS/TEN and the drugs used to manage the rampant HIV epidemic and concomitant upsurge of tuberculosis (TB).⁹ Because of the limited arsenal of effective drugs available to clinicians for treatment, especially for TB, it is often necessary to rechallenge patients.

There are currently no good studies to guide a clinician on how to reintroduce the drugs but the general principles of rechallenging are applicable. Because of the high-risk nature of the reintroduction a few basic conditions have to be met.⁹

- It has to be done in hospital under careful supervision by someone with experience in the management of adverse drug reactions and rechallenges.
- The patient's baseline parameters have to be as close to the pre-morbid state as possible.
- The sequence in which the individual drugs are introduced depends on the known likelihood of the drug to induce SJS/TEN. The drug most likely to have

caused the reaction is introduced last, if at all. If all the other drugs are re-introduced successfully, bar this suspected culprit drug then the assumption can be made that it caused the reaction and the patient does not need to be rechallenged with it.

- The drugs are introduced sequentially and additively. They can be started in small doses which are increased over 3-4 days until normal therapeutic doses are attained. It has to be stressed that this incremental dosing is not a desensitisation regimen, but is based on a theory that the total dose of the drug ingested affects the extent of the disease. There is no evidence at this stage to support this approach or any other for that matter.
- Monitoring is critical to detect any reaction early. The parameters that are monitored are the patient's subjective feelings of being unwell. These can include a sore throat, itchy or burning eyes, itchy skin and fever. Objective changes of the skin and mucosa may lag behind as do abnormal laboratory blood parameters.
- If signs of any reaction are noted then the most recently introduced drug is stopped immediately and the patient is monitored closely. This drug is not re-introduced again. Further alternative drug re-introduction is only resumed once the patient has reached baseline parameters again.
- For tuberculosis rechallenge, the patient must be started on two antituberculosis drugs to which they have not previously been exposed plus the first drug of the rechallenge regimen. This is to avoid the development of resistance. Delay in getting the patient to a full complement of drugs increases the risk of developing resistance.

SUMMARY

SJS and TEN are life-threatening conditions increasingly being seen as a result of the HIV pandemic. Management entails early identification and withdrawal of the offending drug or possible drug(s), transfer to a specialised centre and supportive care employing a multidisciplinary approach. If there is a need for re-introduction of any of the possible medications, it has to be done by experienced clinicians in a hospital setting.

Declaration of conflict of interest

The author declares no conflict of interest.

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