Stevens-Johnson Syndrome

Stevens-Johnson syndrome (SJS) is an immune-complex-mediated hypersensitivity disorder. It ranges from mild skin and mucous membrane lesions to a severe, sometimes fatal systemic illness: toxic epidermal necrolysis (TEN). SJS, SJS/TEN overlap and TEN form a spectrum of severe cutaneous adverse reactions (SCAR) that can be differentiated by the degree of skin and mucous membrane involvement. They are mainly, but not always, caused by drugs. Erythema multiforme (EM) was previously considered to be a milder form of SJS without mucosal involvement; however, the clinical classification defined by Bastuji-Garin in 1993 separates EM as a clinically and aetiologically distinct disorder and has now been accepted by consensus.[1] Erythema multiforme is usually mild (EM minor), with only a few spots, which resolve quickly. The much less common but much more severe type (EM major) can be life-threatening with involvement of the mucous membranes in the mouth, the genital area and on the conjunctiva.

Classification

The classification is based on the percentage of body surface area detached.[2]

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>EM major</th>
<th>SJS</th>
<th>SJS/TEN overlap</th>
<th>TEN with spots</th>
<th>TEN without spots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical targets</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical targets</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Flat</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Macules</td>
<td></td>
<td>✓</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Erythematous</td>
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<tr>
<td>Purpuric</td>
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</tr>
</tbody>
</table>

Distribution of lesions

<table>
<thead>
<tr>
<th>Extent of epidermal detachment</th>
<th>EM major</th>
<th>SJS</th>
<th>SJS/TEN overlap</th>
<th>TEN with spots</th>
<th>TEN without spots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widespread</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Epidemiology

Over a period of 20 years, Bastuji's classification has successfully been in several large epidemiological studies (including RegiSCAR) which have provided reliable information on the incidence of SJS and TEN.[1]

- Incidence is estimated at 2-3 cases/million population/year in Europe.[3]
- It is much more common in individuals with HIV. (Estimated 1-2/1,000 in Canada.)[4]
- It is more common in females than in males.[3]
- Most patients are aged 10-30 but cases have been reported in children as young as 3 months.

Risk factors

The rarity of the disease has made it difficult to clearly ascertain specific risk factors among heterogeneous populations; however, the presence of particular HLA alleles has been found to be associated with SJS/TEN among particular groups - for example:
• HLA B1502 and HLA B1508 among the Han Chinese have been found to be associated with SJS/TEN in reaction to carbamazepine and allopurinol respectively.
• HLA B5701 abacavir is associated with SJS/TEN among people living with HIV.

Screening for these genes among specific populations, before commencing medications, may help to avert occurrence of the disease among these groups.\[5\]

### Aetiology\[^{1,6}\]

Approximately 75% of SJS/TEN are caused by medications and 25% by infections and ‘other’ causes.

### Drugs most commonly associated with SJS and TEN\[^{7,8}\]

- **Allopurinol**
- **Carbamazepine**
- **Sulfonamides:**
  - Trimethoprim-sulfamethoxazole.
  - Sulfadiazine.
  - Sulfasalazine.
- **Antiviral agents:**
  - Nevirapine.
  - Abacavir.
- **Anticonvulsants:**
  - Phenobarbital.
  - Phenytoin.
  - Valproic acid.
  - Lamotrigine.
- **Others:**
  - Imidazole antifungal agents.
  - Non-steroidal anti-inflammatory drugs (oxicam type such as meloxicam).
  - Salicylates.
  - Sertraline.
  - Bupropion (rarely).

### Infection

- **Viral:** includes herpes simplex virus, Epstein-Barr virus, enteroviruses, HIV, Coxsackievirus, influenza, hepatitis, mumps, lymphogranuloma venereum, rickettsia and variola.
- **Bacterial:** includes Group A beta-haemolytic streptococcus, diphtheria, brucellosis, mycobacteria, *Mycoplasma pneumoniae*, tularaemia and typhoid.
- **Fungal:** includes coccidioidomycosis, dermatophytosis and histoplasmosis.
- **Protozoal:** malaria and trichomoniasis.

### Immunisation

Associated with immunisation - eg, measles, hepatitis B.
Presentation[9, 10]

See images available under 'Further reading' section, below.

Symptoms

- It often starts with a nonspecific upper respiratory tract infection, which may be associated with fever, sore throat, chills, headache, arthralgia, vomiting and diarrhoea, and malaise.
- Mucocutaneous lesions develop suddenly and clusters of outbreaks last from 2-4 weeks. The lesions are usually not pruritic.
- Mouth: severe oromucosal ulceration.
- Respiratory involvement may cause a cough productive of a thick purulent sputum.
- Patients with genitourinary involvement may complain of dysuria or an inability to pass urine.
- Ocular symptoms: painful red eye, purulent conjunctivitis, photophobia, blepharitis.

Signs

- General examination: fever, tachycardia, hypotension; altered level of consciousness, seizures, coma.
- Skin:
  - Lesions may occur anywhere, but most commonly affect the palms, soles, dorsum of hands and extensor surfaces. The rash may be confined to any one area of the body, most often the trunk.
  - The rash can begin as macules that develop into papules, vesicles, bullae, urticarial plaques, or confluent erythema.
  - The centre of the lesions may be vesicular, purpuric, or necrotic.
  - The typical lesion has the appearance of a target, which is considered pathognomonic.
  - Lesions may become bullous and later rupture. The skin becomes susceptible to secondary infection.
  - Urticarial lesions are usually not pruritic.
  - Nikolsky sign is positive (mechanical pressure to skin leading to blistering within minutes or hours).

- Mucosal involvement: erythema, oedema, sloughing, blistering, ulceration and necrolysis.
- Eye: conjunctivitis, corneal ulcerations.
- Genital: erosive vulvovaginitis or balanitis.

Differential diagnosis

- Acute generalised exanthematous pustulosis.
- Bullous pemphigoid.
- Bullous phototoxic reactions.
- Chemical or thermal burns.
- Erythroderma.
- Exfoliative dermatitis.
- Maculopapular drug rashes.
- Paraneoplastic pemphigus acantholysis.
- Pemphigus vulgaris.
- Staphylococcal scalded skin syndrome.
- Lyme disease.

Investigations

- Serum electrolytes, glucose and bicarbonate are essential to assess clinical severity and level of dehydration.[9]
- Diagnosis is based on clinical classification - as in the table, above - and on histopathology.
- Skin biopsy: demonstrates that the bullae are subepidermal. Epidermal cell necrolysis may be seen and perivascular areas are infiltrated with lymphocytes.
Management\textsuperscript{[1, 9]}

Multidisciplinary management of eyes, mucous membranes (gynae, mouth, gastrointestinal tract) helps to improve outcomes and reduce adverse sequelae.

- **Acute phase:**
  - Identify and remove causative drug or underlying cause.
  - Use of the ALDEN (Algorithm for assessment of Drug-induced Epidermal Necrolysis) may be useful.\textsuperscript{[11]}

- **A rapid assessment of prognosis should be made using the SCORTEN (Score for Toxic Epidermal Necrolysis) system.** SCORTEN is an illness severity score which has been developed to predict the mortality rate in SJS and TEN. One point is given for each of seven criteria present at the time of admission. The seven criteria are:
  - Age >40.
  - Presence of malignancy.
  - Heart rate >120 beats per minute.
  - Initial percentage of epidermal detachment >10%.
  - Serum bicarbonate <20 mmol/L.
  - Serum urea >10 mmol/L.
  - Serum glucose >14 mmol/L.

- Patients with a SCORTEN score of >3 should be managed in intensive care.
- **Supportive:**
  - Attention to airway and haemodynamic stability.
  - Severe fluid loss may require intravenous fluid replacement and electrolyte correction.
  - Pain control.
  - Skin lesions are treated in the same way as for burns.
  - Mouth: mouthwashes; topical anaesthetics are useful in reducing pain and allowing the patient to take in fluids.
  - Eye care: frequent ophthalmology assessment and frequent eye drops, including antibiotic and steroid when required.
  - Treat secondary infections.
  - **Immunomodulation:**
    - The use of corticosteroids is controversial due to the need to balance dampening of the aberrant immune response with poor healing and increased risk of infection. Some progress has been made with the use of pulsed systemic corticosteroids.
    - Some have advocated ciclosporin, cyclophosphamide, anti-TNFalpha monoclonal antibodies, plasmapheresis, haemodialysis and immunoglobulin therapy in the acute phase; however, none is considered to be standard at this time.\textsuperscript{[1]}

Some reports have found early administration of high-dose intravenous immunoglobulin to be associated with increased mortality in SJS and TEN; this is, therefore, no longer recommended.\textsuperscript{[1]}

**Complications\textsuperscript{[2]}**

- Dehydration and acute malnutrition.
- Shock and multiorgan failure.
- Thromboembolism and disseminated intravascular coagulation.
- Gastrointestinal ulceration, necrolysis, strictures and perforation.
- Skin: secondary infection and scarring.
- Mucosal pseudomembrane formation may lead to mucosal scarring and loss of function of the involved organ system.
- Lung: mucosal shedding in the tracheobronchial tree may lead to respiratory failure.
- Eye complications: include corneal ulceration and anterior uveitis. Sight impairment may develop secondary to severe keratitis or panophthalmitis in 3-10% of patients.
- Vaginal stenosis and penile scarring have been reported.
- Renal complications are uncommon but renal tubular necrolysis and acute kidney injury may occur.

**Prognosis and sequelae\textsuperscript{[1, 9]}**

Many patients surviving SJS and more that 50% surviving TEN experience long-term sequelae involving the skin, mucous membranes or eyes. These include:

- Skin: hyperhidrosis, xeroderma, reversible hair loss, heat and cold sensitivity, scarring and irregular pigmentation.
- Nail dystrophy.
- Mucous membranes: vaginal, urethral and anal strictures. Persistent mucosal erosions.
- Ocular: xerophthalmia, photophobia, symblepharon, synechiae, entropion, meibomian gland dysfunction and sight impairment.

The overall mortality rate is up to 10% for SJS and at least 30% for TEN. However, the mortality rate correlates with the SCORTEN score and is greater than 90% for people with a SCORTEN score of 5 or more.\textsuperscript{[2]} The high mortality rate results primarily from the development of complications in the form of systemic infections and multiple organ failure.\textsuperscript{[12]}
Prevention

- Future avoidance of any possible or confirmed underlying cause. [5]
- Screening for particular HLA alleles in particular groups.

Further reading & references

- UK guidelines for the management of Stevens–Johnson syndrome/toxic epidermal necrolysis in adults; British Association of Dermatologists (2016)
- Stevens–Johnson Syndrome; DermIS (Dermatology Information System)
- Stevens Johnson Syndrome / Toxic Epidermal Necrolysis; DermNet NZ

2. Stevens Johnson Syndrome and Toxic Epidermal Necrolysis; DermNet NZ

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