TENS/STEVENS JOHNSON SYNDROME

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Stevens-Johnson Syndrome is an immune complex hypersensitivity reaction that can be caused from an infection or immune response to drugs. It is a severe expression of a simple rash known as erythema multiforme. SJS is also known as erythema multiforme major. It affects all ages and genders including pediatric populations. The most severe form of SJS is toxic epidermal necrolysis (TENS).
<table>
<thead>
<tr>
<th>Entity</th>
<th>Most common etiologic agent/rash</th>
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<tr>
<td>Erythema multiforme minor</td>
<td>Infectious/classic target lesion without mucous membrane involvement (no epidermal detachment)</td>
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<tr>
<td>Erythema multiforme major</td>
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<tr>
<td>Stevens-Johnson syndrome</td>
<td>Drug induced/widespread purpuric macules and mucosal erosions with 10% epidermal detachment, plus Nikolsky’s sign</td>
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<tr>
<td>SJS/TEN transition</td>
<td>Drug induced/widespread purpuric macules and mucosal erosions with 10%-30% epidermal detachment, plus Nikolsky’s sign</td>
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<tr>
<td>Toxic epidermal necrolysis</td>
<td>Drug induced/widespread purpuric macules and mucosal erosions with more than 30% epidermal detachment, plus Nikolsky’s sign</td>
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**A. Erythema multiforme:** typical targets, with regular round shape, well-defined borders, 3 different zones, predominant on the extremities.

**B, Stevens-Johnson syndrome:** erythematous or purpuric macules with irregular shape and size. Blisters often occur on all or part of the macule. Lesions are widespread. Confluence of individual lesions remains limited, involving less than 10% of the body surface area.

**C, Overlap Stevens-Johnson syndrome–toxic epidermal necrolysis:** confluent blisters result in detachment of the epidermis and erosions on 10% to 29% of the body surface area.

**D, Toxic epidermal necrolysis:** widespread detachment of epidermis on more than 30% of the body surface area.
Mucosal involvement is prominent and severe, although not forming actual blisters. At least 2 mucosal surfaces are affected including:

- **Eyes (conjunctivitis)** – red, sore, sticky
- **Lips/mouth (cheilitis, stomatitis)** – red crusted lips, mouth ulcers
- **Oesophagus** – causing difficulty eating
- **Upper respiratory tract (trachea and bronchi)** – causing cough and respiratory distress
- **Genital area and urinary tract** – ulcers
- **Gastrointestinal tract** – causing diarrhoea.
SCORTEN is an illness severity score that has been developed to predict mortality in SJS and TEN cases. One point is scored for each of seven criteria present at the time of admission. The SCORTEN criteria are:

- Age >40 years
- Presence of a malignancy (cancer)
- Heart rate >120
- Initial percentage of epidermal detachment >10%
- Serum urea level >10 mmol/L
- Serum glucose level >14 mmol/L
- Serum bicarbonate level <20 mmol/L

The risk of dying from SJS/TEN depends on the score.

<table>
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<th>SCORTEN predicted mortality rates</th>
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<td>SCORTEN 0-1</td>
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<tr>
<td>SCORTEN 2</td>
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<td>SCORTEN 3</td>
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<td>SCORTEN 4</td>
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<td>SCORTEN 5 or more</td>
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AETIOLOGY

- Infectious
- Drug-induced
- Malignancy-related
- Idiopathic
Viral diseases that have been reported to cause Stevens-Johnson syndrome include the following:

- Herpes simplex virus (possibly; remains a debated issue)
- AIDS
- Coxsackie viral infections
- Influenza
- Hepatitis
- Mumps
- In children, Epstein-Barr virus and enteroviruses have been identified. More than half of the patients with Stevens-Johnson syndrome report a recent upper respiratory tract infection.
Bacterial etiologies include the following:

- Group A beta-hemolytic streptococci
- Diphtheria
- Brucellosis
- Lymphogranuloma venereum
- Mycobacteria
- Mycoplasma pneumoniae[11, 12]
- Rickettsial infections
- Tularemia
- Typhoid

Possible fungal causes include coccidiodomycosis, dermatophytosis, and histoplasmosis. Malaria and trichomoniasis have been reported as protozoal causes.
Antibiotics are the most common cause of Stevens-Johnson syndrome, followed by analgesics, cough and cold medication, NSAIDs, psychoepileptics, and antigout drugs. Of antibiotics, penicillins and sulfa drugs are prominent; ciprofloxacin has also been reported.
The following anticonvulsants have been implicated:

- Phenytoin
- Carbamazepine
- Oxcarbazepine (Trileptal)
- Valproic acid
- Lamotrigine
- Barbiturates

Mockenhapupt et al stressed that most anticonvulsant-induced SJS occurs in the first 60 days of use.
Antiretroviral drugs implicated in Stevens-Johnson syndrome include nevirapine and possibly other non-nucleoside reverse transcriptase inhibitors. Indinavir has been mentioned.
Stevens-Johnson syndrome has also been reported in patients taking the following drugs:

- Modafinil (Provigil)
- Allopurinol
- Mirtazapine[17]
- TNF-alpha antagonists (eg, infliximab, etanercept, adalimumab)
- Cocaine
There is strong evidence for a genetic predisposition to severe cutaneous adverse drug reactions such as Stevens-Johnson syndrome. Carriage of the following human leukocyte antigens has been associated with increased risk:

- HLA-B*1502
- HLA-B*5801
- HLA-B*44
- HLA-A29
- HLA-B12
- HLA-D1R7
- HLA-A2
- HLA-B*5801
- HLA-A*0206
- HLA-DQB1*0601
In the United States, the annual frequency of TENS is reported to be 0.22-1.23 cases per 100,000 population. In the HIV-positive population, the incidence of TENS increases to 1 case per thousand per year.

Worldwide, the average annual incidence of TENS is 0.4-1.3 cases per million population. In 1992, the cumulative incidence of TENS and SJS in Germany was 1.9 cases per million population. A French survey of dermatologists and health care facilities reported an annual incidence of 1 case per million population.
For unclear reasons, TENS appears to have a predilection for females. The female-to-male ratio is 1.5:1.

TENS may occur in all age groups; however, the mean age of patients with TENS is reported to be between 46 and 63 years. Infection is more commonly implicated as an etiology in children, whereas medication exposure is more common in adults. Elderly persons may be at greater risk because of their tendency to use multiple medications.
The mortality is almost 10% for patients with SJS, approximately 30% for patients with SJS/TENS-overlap and almost 50% for patients with TENS. For SJS, SJS/TEN-overlap and TENS together the mortality rate is almost 25
TENS is believed to be an immune-related cytotoxic reaction aimed at destroying keratinocytes that express a foreign antigen.

TENS mimics a hypersensitivity reaction, with its characteristic delayed reaction to an initial exposure and an increasingly rapid reaction with repeated exposure.
Exact mechanism is unknown; however, one theory holds that altered drug metabolism in some patients causes formation of reactive metabolites that bind to and alter cell proteins, triggering a T-cell–mediated cytotoxic reaction to drug antigens in keratinocytes.
CLINICALLY MANIFESTS IN THREE STAGES:

- Crescendo
- Critical
- Convalescent
- Lasts for 2-3 days before onset
- Generalised complaints:
  - Fever
  - Malaise
  - Rhinitis
  - Anorexia
  - Pharyngitis

CRESCENDO PHASE
- Persistent fever
- Mucosal & Cutaneous sloughing
- Erythema and blisters
- Generalised sloughing

CRITICAL PHASE: (8-12 DAYS)
**OCULAR (40-50%)**

- Conjunctivitis
- Photophobia
- Alternations in visual acuity
- Corneal opacities
- Corneal ulcerative lesions
- Scarring around eyelids
- Blindness

**MULTISYSTEM MANIFESTATIONS**
• Sore throat
• Pharyngitis
• Pneumonitis
• Pneumonia
• ARDS
• Respiratory failure
• Pulmonary embolism
GASTRO-INTESTINAL:

- Anorexia
- Gastritis
- Mucositis
- Stomatitis
- Gastro-intestinal bleeding
- Necrotic bowel
GENITO-URINARY

- Dysuria
- Anuria
- Urinary retention
- Urinary tract infection
- Renal failure
INTEGUMENTARY: (Most affected system)

- Loss of skin integrity
- Wound infections
- Hypopigmentation
- Hyperpigmentation
- Hypertrophic scarring
- Wound contracture
METABOLIC:
Increase in basal metabolic rate

IMMUNE:
- Fever
- Localised infections
- Systemic infections
- Systemic inflammatory response syndrome
- Multiple organ dysfunction syndrome
PSYCHOSOCIAL:

- Anxiety
- Pain
- Fear
- Powerlessness
- Altered body image
- Knowledge deficit of disease process
Cessation of sloughing
Re-epithelialization
Healing of skin and mucous membranes

CONVALESCENT PHASE
Duration of convalescent phase dependent on:

- Location and extent of involvement
- Presence of systemic infections
- Trauma to sloughing tissue
- Other complications
TREATMENT

- Early recognition
- Referral to burn centre
- Cessation of use of drug
- Highly specialised nursing care
- Interdisciplinary team approach
ESSENTIAL ASPECTS

- Fluid resuscitation
- Treatment for alterations in skin
- Control of infection and sepsis
- Pain management
- Nutritional therapy
- Psychosocial support
- Rehab services
Controversial

- Corticosteroids
- IV Immunoglobulin
- Immuno-modulating agents
- N-acetylcystine
• Meticulous eye care every 1-2 hrs
• Saline rinses
• Liberal lubrication of conjuntiva
• Daily visits by ophthalmologist

OCULAR
• Aggressive hygiene
  suctioning
  turning
  incentive spirometry
  therapeutic bronchoscopy

• Endotracheal intubation

• Mechanical ventilation to improve oxygenation

PULMONARY
• Nutritional consultation
• Soft diet
• Frequent oral rinses
• Antacid therapy
• Soft, flexible tubing
• Stool softeners

GASTRO-INTESTINAL
• Renal failure
• UTI
• Urinary catheterization
 Prompt debridement
  • prevent infection
  • facilitate healing

 Meticulous wound care
  • cleansing
  • mechanical debridement
  • dressing
  • antimicrobial dressings
  • biological dressings
Risks of hypothermia

Control of pain and anxiety

- extensive sloughing
- exposed nerve endings
Pigment change – patchwork of increased and decreased pigmentation
Skin scarring, especially at sites of pressure or infection
Loss of nails with permanent scarring (pterygium) and failure to regrow
Joint contractures
Scarred genitalia – phimosis (constricted foreskin which cannot retract) and vaginal synechiae (occluded vagina)
Serious eye problems, which can lead to blindness. This is the most important of the long term complications. These include:
Dry and/or watery eyes, which may burn and sting when exposed to light
Conjunctivitis: red, crusted, or ulcerated conjunctiva
Corneal ulcers, opacities and scarring
Symblepharon: adhesion of conjunctiva of eyelid to eyeball
Ectropion or entropion: turned-out or turned-in eyelid
Trichiasis: inverted eyelashes
Synechiae: iris sticks to cornea

Long term implications
36-year old, female patient
15 year history of depression

Fourteen day history of use of:
- Tegretol 200mg bd
- Alzam
- Remeron 30mgs nocte
- Seroquel 50 mgs nocte
- Zopidem 7.5mgs nocte

CLINICAL CASE STUDY
Presents with:
- 2 day history of rash
- Temperature 39 degrees
- Nausea
- Swelling and Redness of eyes
- Redness of Throat

Admitted to Surgical ICU on 12 September 2003
Shortly after admission:

- Diffuse bullae
- Consistent fever
- Marked desquamation of skin
14th September (Day 2)

- Heparin (DVT)
- Enteral feeds
- Rehydration
- Blood-stained urine
- Eyes: artificial tears + Voltaren drops
- Ulceration of the mouth
Marked diarrhea
  • CVP inserted

Plastic surgeon involved

Confirmed diagnosis:
  • Stevens-Johnson Syndrome
  • Drug reaction to Tegretol
  • TENS

17th September (Day 5)
• Tracheotomy performed
• Debrided
• Acticoat
• New CVP
• New A-line

30 September 2003 (Day 18)
6th October (Day 24)

- Candida Prapsilosis
- Fever
- Oozing from mouth
- Lungs affected
- Muscle relaxant to improve ventilation
- Coagulase neg Staphylococcus
- Pseudomonas specimen
- Tracheotomy tube changed
- To larger diameter
- Debride
- Acticoat
17 October 2003 (Day 35)

- Debride
- Acticoat
- Bactroban face, lower legs
18th of October (Day 36)

3 Further units of packed cells
23% band forms
6% metamyelocytes
5% meylocytes
1% promyelocytes
CVP 14-15
Ongoing septicaemia
24th October (Day 42)

- Hb 7
- Oozing settled
- Nasogastric feeding
- Debride
- Acticoat
- Bactroban
27th October (Day 45)

- E.coli
- Beta group Streptococcus
- No active bleeding
- Urine output maintained
- Temperature normal
12th November (Day 61)

- Temperature
- Pseudomonas
- Generalised weakness
- Poor vital capacity
- Continued ventilation
- Profuse diarrhea
- Distended abdomen
13 November (Day 62)

- Abdominal pain
- Distension
- Enlarged liver
- Pancreatitis with raised lipase
16 November (Day 65)

• Lasix for oedema
• Jaundiced
• Stenotrophomonas
• Pseudomonas
• CJ tube removed
• Nasal oxygen
• Chest clear left, improved right
• Temperature normal
• Blood pressure normal
• Lost peripheral oedema
• Abdomen softer
• Jaundiced
• 4 finger hepatomegaly
• Nasogastric feeding
• No diarrhea
• Difficulty swallowing
• Fully mobilised
19 December 2003 (Day 98)

- Discharged from hospital
- Left vocal cord paralysis
- Mild degree laryngeal incoordination
- Soft diet
- Cough reflex good