



DRUG ALERT

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STEVENS- JOHNSON SYNDROME

Stevens-Johnson syndrome (SJS) is an uncommon, severe, mucocutaneous blistering disorder with an acute and unpredictable onset causing considerable morbidity. It's more severe form is called toxic epidermal necrolysis (TEN). Previously, SJS was considered as erythema multiforme (EM) major but now is considered distinct from EM on the basis of severity, presence of constitutional signs, atypical target lesions with tendency to confluence, positive Nikolsky's sign, more than one mucosal site involvement and residual sequelae.

Definition and classification

In 1993, the following consensus classification of acute bullous disorders that are attributed to drugs or infectious agents has been proposed:

1. *Bullous EM*: Epidermal detachment below 10% of body surface area (BSA) with typical localized target lesions or "raised atypical targets."

2. *SJS*: Epidermal detachment below 10% of body surface area with widespread erythematous or purpuric macules or flat atypical targets.

3. *Overlap SJS-TEN*: Epidermal detachment between 10% and 30% of body surface area with widespread purpuric macules or flat atypical targets.

4. *TEN with spots*: Epidermal detachment above 30% of body surface area with widespread purpuric macules or flat atypical targets.

5. *TEN without spots*: Epidermal detachment above 10% of body surface area in large epidermal sheets and without purpuric macules or target-like lesions.

Incidence and epidemiology

The average incidence of SJS and TEN are estimated at 2.6 to 7.1 and 1.2 cases per million per year respectively. There is no ethnic preponderance; females appear to be about twice as frequently affected as males. Children are less often affected.

Table 1. Drugs causing Stevens Johnson Syndrome

Group	Name of drugs
Antimicrobials	Sulfonamides, co-trimoxazole, thiacetazone, amoxicillin, ampicillin, ethambutol, isoniazid, erythromycin, azithromycin, clindamycin, ciprofloxacin, levofloxacin, grepafloxacin, ofloxacin, chloroquine, streptomycin
Anti-convulsants	Carbamazepine, phenytoin, fosphenytoin, lamotrigine, phenobarbital
Anti-fungals	Griseofulvin, fluconazole, itraconazole
Gastro-intestinal drugs	Famotidine, omeprazole, ranitidine
NSAIDs	Oxybutazone, valdecoxib, salicylates, fenbufen, isoxicam, ibuprofen, sulindac,
Miscellaneous	Allopurinol, nevirapine, chlorpromazine, cocaine, tramadol, dapsone, gold, nitrofurantoin, tolbutamide, pentamidine, verapamil, amiodarone, methylprednisolone, prednisolone

The incidence is dramatically increased in the patients with SLE and HIV-infected population. SJS-TEN has been found to be associated with the HLA-A29 and HLA-B12 (relative risk-13.4) and DR7 haplotypes. Although SJS is listed as a rare disease, it may be more prevalent than previously thought.

Etiology

Drugs account for more than 50% cases of SJS and 80-95% of TEN cases. Infectious agents (*Herpes simplex* and *Mycoplasma pneumoniae* mainly), immunizations, and graft versus host disease (GVHD) are also implicated, particularly in SJS. Around 5% cases may be idiopathic or triggered by unidentified infectious agents.

Causative drugs: More than 100 drugs have been associated (Table 1) with the development of SJS/TEN in single case reports or retrospective studies. Sulfa drugs particularly long acting sulfonamides and cotrimoxazole are cited as most common in most surveys and reviews. Anticonvulsive drugs such as phenytoin, carbamazepine, and phenobarbital seem to

FIRST EVER INHALATIONAL INSULIN IS APPROVED BY FDA

Food and Drug Administration (FDA), USA has approved the first ever inhalational insulin on 27th Jan 2006. It is marketed as Exubera by Pfizer. Exubera eliminates the need for meal-time insulin injection in diabetic patients. Peak insulin concentration is attained faster than regular insulin. Its use is contraindicated in smokers, bronchitis, emphysema and bronchial asthma.

carry equally high risks; their relative risks were calculated to be from 11 to 15. In contrast to this, carbamazepine was found to elicit the highest incidence of SJS-TEN per user (14 per 100,000). Antibiotics are often prescribed at the onset of fever and may be mistaken for cause when the mucocutaneous eruption appears. Patients are at greater risk of this type of drug reaction during the first 4 weeks of therapy, usually between 1-3 weeks. When SJS or TEN develops within a few days or after months of starting a drug, a causal link is less convincing. There is no standardized laboratory test to confirm drug aetiology. Determination of cause is based on the evaluation of probability, considering both the nature of drug and timing of reaction (temporal association).

Pathogenesis

The pathogenesis of SJS and TEN is not well understood. In drug induced disease, a widely accepted theory is that accumulation of drug metabolites in the epidermis induces an immunologic response that results in cell death and epidermal necrolysis. Affected individuals are believed to have a genetically determined inability to detoxify drug metabolites. There is evidence that cell-mediated cytotoxicity, analogous to graft versus host disease (GVHD) also plays its role. Evidence for apoptosis has been attributed to expression of active Fas ligand on TEN keratinocytes. Fas ligand interacts with Fas (CD95), a death receptor on the cell surface of keratinocytes, and the interaction causes apoptosis.

Clinical features

Both SJS and TEN are preceded by **prodromal signs** of high fever, cough, sore throat, and general malaise. The prodrome may last from one to several days, during which time an infectious illness is often suspected and antibiotic and antipyretic agents are prescribed. In cases of mycoplasma-induced SJS, the preceding fever and cough can be of longer duration and there may be radiographic evidence of atypical pneumonia. The mucous membranes are involved in all cases of SJS and in 85% to 95% of patients with TEN.

Initial swelling and erythema are followed by blistering and ulceration of **lips and oral mucosa**. The mouth lesions are extremely painful. In mild cases, patient may continue to accept oral fluids and nutrition but majority are unable to eat or drink for 1 to 2 weeks. The nasal mucosa may also be affected. **Conjunctivitis** varies in severity from mild inflammation to severe eyelid swelling, conjunctival erosions, purulent exudate, and pseudomembrane formation. **Genital** erosions are not invariably present but when severe, may result in blistering vulvovaginitis or urethral and anal erosions. Other mucous membranes, such as esophagus,

intestinal tract and respiratory epithelium are less frequently affected.

The **cutaneous** eruption of SJS develops rapidly. Erythematous lesions evolve over days into purpuric macules, target lesions (individual lesions less than 3 cm in diameter with a regular round shape, well-defined border, and at least 3 different zones, that is, 2 concentric rings around a central disk. One ring consists of palpable edema, paler than the center disk), atypical target-like lesions, bullae, and erosions on the face, ears, trunk, and limbs, including the palms and soles. Drug-induced SJS is usually associated with extensive skin disease. The eruption appears as diffuse, painful facial erythema and a morbilliform exanthem or atypical target-like lesions and purpuric macules. Vesiculation and painful erosions develop within days and are variable in extent. The eruption may become confluent with progression to sheet like loss of epidermis in some areas.

The **average duration** of disease is 2 weeks with fever, malaise, systemic symptoms and appearance of mucocutaneous eruptions in first 4-10 days and gradual **improvement and healing** during the next 1-2 weeks.

In TEN/SJS overlap, extensive skin loss and acute complications can result in a more prolonged and life threatening illness. Confluent areas of inflammation produce large areas of blistering and sheet like epidermal detachment. Nikolsky's sign is positive, and the underlying denuded skin is red and exquisitely tender.

Laboratory Investigations

SJS-TEN is invariably accompanied by an elevated blood sedimentation rate and may show moderate leukocytosis, fluid-electrolyte imbalances, microalbuminuria, hypoproteinemia, elevation of liver transaminases and anemia. Neutropenia occurs in a minority of cases and is then regarded as an unfavorable prognostic sign. Other laboratory abnormalities depend on the severity of other systems involvement

Differential diagnosis

During the prodrome and early stages, both SJS and TEN may be misdiagnosed as an **infectious illness**. A drug eruption should always be considered in a child in whom an exanthema and fever develops shortly after initiating drug treatment. Prior to confluence and vesiculation, SJS-TEN may be confused with other **morbilliform drug eruptions**. Fixed drug eruptions especially at mucocutaneous junction can sometimes resemble SJS. In **Kawasaki disease**, like SJS, there may be intense mucosal erythema, but Kawasaki disease can be distinguished from SJS by the absence of oral erosion and swollen blistered lips, usually evident even in the early stages of SJS. **Paraneoplastic pemphigus**, a rare disorder can

closely mimic SJS with oral erosions and extensive bullous skin disease. Skin necrosis and severe oral and genital ulcerations can occur after high dose of methotrexate therapy resembling SJS/TEN. **Staphylococcal scalded skin syndrome** in children is characterized by subcorneal blisters rather than full thickness skin necrosis and does not involve mucous membrane. In cases of **scalding, kerosene or paraffin burns and exposure to caustic agents** the differential diagnosis rests on artificial distribution, absence of a preceding rash and lack of skin appendage involvement.

Management

Identification of provocative agent should be attempted. All potentially **culpable drugs** should be withdrawn. The **mainstay of treatment** is supportive care till epidermis regenerates and prevention of acute complications like sepsis, fluid electrolyte imbalance, upper airway obstruction due to mucosal sloughing and edema, pneumonia, urinary retention, renal shutdown, hypovolemia, prevention of synechia formation (by ocular lubricants, sweeping of conjunctival fornices, and removal of fresh adhesions, etc.), maintaining nutrition (high-calorie and high-protein diet), oral hygiene, reverse barrier dressing and pain management.

Routine antibiotics are not indicated unless there is evidence of infection as fever may be part of disease process. Use of systemic glucocorticoids is controversial. It may be used in the early stages of drug-induced SJS-TEN. Doses ought to be tapered quickly but cautiously. Debridement of necrotic skin should not be performed before disease activity ceases.

Topical treatment may be carried out with gauze dressings. Patients should be placed on aluminum sheets or low pressure mattresses. Dramatic improvement in

both SJS-TEN has been reported with use of **intravenous immunoglobulin (IVIg)**, 0.2 to 0.75 g/kg body weight. **Alternative systemic treatment methods** for the acute phase of SJS-TEN include hemodialysis, plasmapheresis, cyclophosphamide, and cyclosporine. Granulocyte colony-stimulating factor has been recommended for the treatment of severe SJS-TEN with neutropenia.

Course and prognosis

The prognosis correlates directly with the extent of epidermal detachment. The mortality rate of SJS-TEN depends on the severity of the disease and the quality of medical care; it is low for SJS (5%), SJS-TEN overlap (10-15%) and ranges from 30-40% in TEN. Septicemia, gastrointestinal hemorrhage, pneumonia, and fluid and electrolyte imbalance leading to renal insufficiency are the major complications leading to death. Recovery is slow, healing may require from 3 to 6 weeks or more.

Key points

Suspect SJS if the patient has the following features:

- History of systemic medications prior to the onset of rash
- Rash with fever and burning or blistering of the mucous membranes, i.e.: mouth, eyes, nose and genital area.
- Appearance of target lesions on the skin
- Toxic features in the patient

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Drug induced SJS, TEN and EM reported to RPC(South), JIPMER, Pondicherry during April to December, 2005

<i>Pharmacovigilance centre</i>	<i>No. of ADRs</i>	<i>Suspected drugs</i>
AI-Ameen College of Pharmacy, Bangalore	14	Phenytoin, carbamazepine, diclofenac, nimesulide, paracetamol(3), ampicillin, allopurinol, frusemide, ranitidine(2), levocetirizine, pentoxiphylline
JSS Medical College and Hospital, Mysore	7	Sparfloxacin, penicillin, diclofenac, amoxycillin, ciprofloxacin, phenytoin, acyclovir
Manipal College of Pharmaceutical Sciences, Manipal	7	Ciprofloxacin, paracetamol, cotrimoxazole, penicillin, streptomycin, INH, phenolphthalein
Amritha Institute of Medical Sciences, Kochi	6	Phenytoin, roxithromycin, carbamazepine(3), lamotrigine
JIPMER, Pondicherry	3	NSAID, prednisolone, adriamycin
PSG Institute of Medical Sciences, Coimbatore	2	Carbamazepine(2)
Sri Devaraj Urs Medical College, Kolar	1	Carbamazepine

*Numbers in bracket refer to the number of times the drug has caused the ADR

List of some drugs/formulations recently approved by DCGI, Govt. of India

Nitazoxanide (500 mg) + Ofloxacin (200mg) Tablet	Nitazoxanide: Antiparasitic agent effective against a wide variety of protozoa and helminths. Oral bioavailability is good and well tolerated, with mild gastrointestinal side effects. Used in Giardia intestinalis-induced diarrhoea in patients \geq 1 year of age and Cryptosporidium-induced diarrhea in children aged 1-11 years. (Clin Infect Dis 2005; 40:1173-80) Ofloxacin: More effective against gram-negative organisms than gram-positive ones
Calcium Polycarbophil (500 mg) Tablet	Improves colonic transit and relieves abdominal pain in Inflammatory bowel syndrome (IBS). (Hepatogastroenterology 2005; 52:1416-20)
Erlotinib Hydrochloride (25mg/100mg/150mg)Tablet	It is a <i>Tyrosine kinase inhibitor</i> , approved by the US FDA in November 2004 for the treatment of advanced non-small-cell lung cancer after failure of at least one prior chemotherapy regimen. It is an anticancer drug that inhibits the activity of the epidermal growth factor receptor. (Nat Rev Drug Discov 2005;Suppl:S14-5)
Olmesartan Medoxomil (5mg/20mg/40mg) Tablet	Cardioprotective due to suppression of inflammatory cytokines and cytotoxic myocardial injury in addition to hemodynamic modifications. (Am J Physiol Heart Circ Physiol 2005;289:H1147-52)
Feropenem Sodium (150mg/200mg) Tablet	An oral penem, unique among carbapenems and other available beta-lactams, with broad spectrum activity, could be used as empirical treatment in infections due to unidentified anaerobes. (J Chemother 2005 ;17:36-45)
Levodopa (50 mg/100 mg/150 mg) + Carbidopa (12.5 mg/25 mg/37.5 mg + Entacapone (200 mg) tablet	Prolongs the duration of action of dopamine by preventing its metabolism. Used in Parkinson's disease
Bivalirudin Injection (250mg/vial)	A short-acting direct thrombin inhibitor used as an anticoagulant in PTCA (percutaneous transcatheter coronary angioplasty) and cardiac surgical patients with heparin-induced thrombocytopenia (HIT) or suspected HIT. (J Extra Corpor Technol. 2005; 37:296-302)
Feracrylum (1%) + Metronidazole (1%) gel	Feracrylum: A water-soluble polymer of polyacrylic acid with hemostatic property. Also got antimicrobial activity against a wide variety of microorganisms and its efficacy is comparable to that of povidone-iodine. (Indian J Pathol Microbiol. 2001; 44:431-3) Metronidazole: A nitroimidazole with antibacterial activity against a wide variety of anaerobic pathogens including both gram positive and gram negative organisms. Combination used as antiseptic gel.
Efavirenz Oral Solution (30mg/ml)	Third non-nucleoside, reverse transcriptase inhibitor approved by FDA. Used in HIV infection.

GUIDELINES FOR REPORTING OF ADVERSE DRUG REACTIONS

Regional Pharmacovigilance Centre, JIPMER, Pondicherry invites reports of all suspected adverse reactions to drugs and other medicinal substances, including herbals, traditional and complementary medicines, blood products, medical devices and vaccines.

REPORT EVEN IF:

- The drug is an established one and the adverse drug reaction is well known
- You are not certain the product caused adverse event
- You don't have all the details

WHO CAN REPORT:

Any health care professional (doctors including interns, residents, dentists, nurses and pharmacists)

WHERE TO REPORT: You can report online at www.jipmer.edu or send your reports to:

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Department of Pharmacology, JIPMER, Pondicherry-605006.
Phone: 2272380; Ext: 3308/3301; E-mail: www.jipmer.edu

Note: If you are at JIPMER you can also use the yellow forms provided in wards.