IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 9, Issue 9 Series. II (September 2019), PP. 18-38 *www.iosrphr.org*

A Review on Steven Johnsons Syndrome: Hypersensitivity Reaction

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Received 18 September 2019; Accepted 04 October 2019

Abstract: Stevens-Johnson syndrome (SJS) is a rare immune-complex–mediated type-IV hypersensitivity reaction that primarily affects the skin and the mucous membranes leading to cell death or cell apoptosis. The etiology of this disorder is multiple, including drugs in almost 75% of cases, infectious agents, genetic predisposition and idiopathic causes account for 25% of cases. It is characterized by skin and mucous membrane reactions potentially fatal result from hypersensitivity to precipitating factors, such as infections by viruses, fungi, bacteria, diseases of the connective tissue, malignant neoplasms, multiple vaccines and medicines. Stevens-Johnson syndrome is a form of a life –threatening skin conditions, in which cell death causes the epidermis to separate from the dermis. This syndrome is thought to be a hypersensitivity complex that affects the skin and the mucous membranes. It is more common in female than males.Most patients are aged 10-30 but cases have been reported in children as young as 3 months. Patients may complain of a burning rash that begins symmetrically on the face and the upper part of the torso. An idiosyncratic, delayed hypersensitivity reaction has been implicated in the pathophysiology of Stevens-Johnson syndrome.The clinical symptoms that are considered to confirm the diagnosis are areas of erythematous and macules on skin that shows Nikolsky sky sign upon the mechanical pressure. No specific treatment of Stevens-Johnson syndrome is noted; therefore, most patients are treated symptomatically. Patients should be treated with special attention to airway and homodynamic stability, fluid status, wound/burn care, and pain control.

Key Words: Steven Johnson syndrome,type-IV hypersensitivity,malignant neoplasms.

I. INTRODUCTION

Stevens-Johnson Syndrome (SSJ) can be defined as a framework of an acute inflammatory disease pathophysiological, feverish and self-limiting, lasting approximately two to four weeks, which affects the skin and the mucous membrane. The syndrome usually begins after the use of medications or occurrence of infections and probably introduces autoimmune pathogenesis1.

Stevens-Johnson syndrome (SJS) is a rare immune-complex–mediated type-IV hypersensitivity reaction that primarily affects the skin and the mucous membranes leading to cell death or cell apoptosis29,30. Mucosal,conjunctival, and anogenital mucous membranes are prominently affected by SJS31. SJS is clinically similar to many severe cutaneous diseases but it differs in some or the other way. SJS and toxic epidermal necrolysis(TEN) are similar clinically and pathologically but differ only by severity of diseases and were within the same spectrum i.e., severe cutaneous adverse reactions (SCAR). Although different in clinical pattern, prognosis and etiology, erythema multiform with mucosal involvement, is also part of this spectrum32. The other diseases that includes in this spectrum are acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms complex (DRESS). At first in early days (before 1922) SJS was described as an generalised epidermal eruption. These epidermal eruptions may range from transient erythema to life threatening SCAR33.

The terminology of these different diseases has been conflicted for several years; the differentiation has been made after a consent definition was proposed in 1993. This definition differentiated theErythema multiforme major(EMM) from SJS, TEN and SJS overlap TEN32. This is also useful in distinguishing the cases clinically that helps in treating the patients appropriately and also as standard for many other studies. This classification categorise the diseases into 5 types like Bullous erythema multiform, Steven Johnson's syndrome, Overlap SJS-TEN, TEN with spots and TEN without based on some disease characteristics like pattern of

lesions, extent of epidermal surface involved or the Body surface area (BSA) effected32,34.Clinically SJS is characterised by fever, inflammation of the buccal mucosa, and severe purulent conjunctivitis29. SJS and TEN are characterized by cutaneous erythema with blister formation of various extent and haemorrhagic erosions of mucous membranes. Fever and malaise are the first symptoms of the disease32.In paediatric patients, SJS is usually accompanied or associated with other comorbidities like ocular infections or inflammation, blindness, viral or bacterial infections, pneumonia etc35.

The aetiology of this disorder is multiple, including drugs in almost 75% of cases, infectious agents, genetic predisposition and idiopathic causes account for 25% of cases29,32. The different etiological factors will be discussed in later sections of this review. Identification of the cause is important for the individual patient as it reflects the main stay of therapy. Therapeutic outcomes may be poor in severe disease conditions and the mortality rate is usually higher in these cases. The mortality and disease progression of a particular patient varies with the severity of the disease, age of the patient, the underlying cause and therapeutic options32.

It is characterized by skin and mucous membrane reactions potentially fatal result from hypersensitivity to precipitating factors, such as infections by viruses, fungi, bacteria, diseases of the connective tissue, malignant neoplasms, multiple vaccines and medicines. The oral mucosa, conjunctiva and lips are the main regions involved.The eye frame is characterized by a purulent catarrhal conjunctivitis, diphtheritic membranous or bilateral.In the chronic phase, most patients present numerous amendments of the ocular surface that may compromise visual acuity, highlighting, trichiasis, dry eye, corneal conjunctivitis and keratinization2.The incidence of SSJ is estimated between 1 to 6 cases per one million inhabitants. Although rare, thiscondition generates a strong emotional, social and economic impact, because it is a chronic entity thatpotentially leads to blindness in young patients2.

The treatment of Stevens-Johnson Syndrome is usually symptomatic and support: meticulous care must be made with the skin and mucous membrane, similar to a burn patient, in addition to daily and follow-up ophthalmologic evaluation for long term. In addition, you must perform the suspension or replacement ofthe use of drugs that have been linked to the appearance of skin lesions1.

Although the Stevens-Johnson Syndrome is a pathological phenomenon of rare occurrence, presents serious implications that can endanger the patient's life. It is important that the professional be aware of the initial manifestations of this type of Pathology, in order to achieve early diagnosis and, along with the medical staff, can request the return or interruption of use of medication promoter of Pathology, thus decreasing the likelihood of progression to a more serious, or even death3.

Stevens-Johnson Syndrome is often associated with the use of carbamazepine (CBZ) a well-tolerated anticonvulsant, used to ease the pain of the herpes zoster (HZ), which has as its main complication to post-herpetic neuralgia, thus resulting in severe skin reactions. These are considered immunereactions to medication and can be characterized as hypersensitivity syndrome due to seniority of immunological abnormalities to the drug. It presents clinically with erythema, necrosis and extensive epidermal detachment, mucosal involvement and systemic symptoms. The rapid diagnosis knowledge becomes essential, because the withdrawal of the drug is often the most important action to minimize the resulting morbidity4.

Several studies show that medicines are important resources for health recovery, once that improve healthand treat disease, and could promote confidence and participation in the services. However, the use of medicines presents risks. Even with the strict criteria of protection and safety, which are required by the Ministry of health, several factors expose users to unwanted effects caused by medicines3.

The adverse drug reaction (ADR) is among the 10 leading causes of mortality. Despite the advancement of pharmacovigilance in the world, the adverse effects, known or not, of medicines marketed still carry great impact to the health of individuals. For this reason, it is of great significance to rational use of medicines5.The proper use of medicines, also called for rational use of medicines (RUM), includes appropriate indication to the situation, distribution/dispensing clinic according to the individual needs and administration/correct use6.

Access to medicines, in turn, indicates the relationship between the need for medicines and supply them with quality7. Access is the first component of the URM. In the hospital environment, the activities carried out by various pervades URM departments/sectors/services involving different professional categories8. The term adverse event (and) the appearance of a health problem caused by the care and not the underlying disease, resulting in temporary or permanent incapacity, and can even evolve into death. Many adverse events originate from surgical procedures, use of medications, medical procedures, delay or inaccuracy in the diagnosis9.You can tell, from the concept of adverse event to medicine (EAM), which for the pharmacologicaltreatment have the desired effect should consider both the effectiveness and the safety of the medicinal product as all procedures involved in the process. Then arises the need to differentiate the componentresponsible for the EAM10.

The MSA are sub-divided into two groups. The first, called adverse reactions to medicines, relates to therisk inherent in front of the appropriate use of medicines, therefore, inevitable. The other, set to medication

errors, understood as any preventable event, arising from the improper use or non-use of needed medicines, therefore, possibly related to failure1.

The reality leaves no doubt as to the importance of identifying and knowing the adverse reactions to medicines, with the objectives to prevent and reduce morbidity and mortality related to them. This purpose will be achieved with the participation of health professionals, of the regulation, control and supervision and enterprises involved in the production and marketing of medicines in the monitoring of reactions11.

DEFINITION:

Stevens-Johnson syndrome is a form of a life –threatening skin conditions, in which cell death causes the epidermis to separate from the dermis. This syndrome is thought to be a hypersensitivity complex that affects the skin and the mucous membranes. The exact etiology and treatment at this time is not well understood. The most common causes for initiation of the syndrome are the use of certain antibiotics such as sulfa drugs. Stevens-Johnson syndrome (SJS) is a moderate form of toxic epidermal necrolysis (TEN)[36].

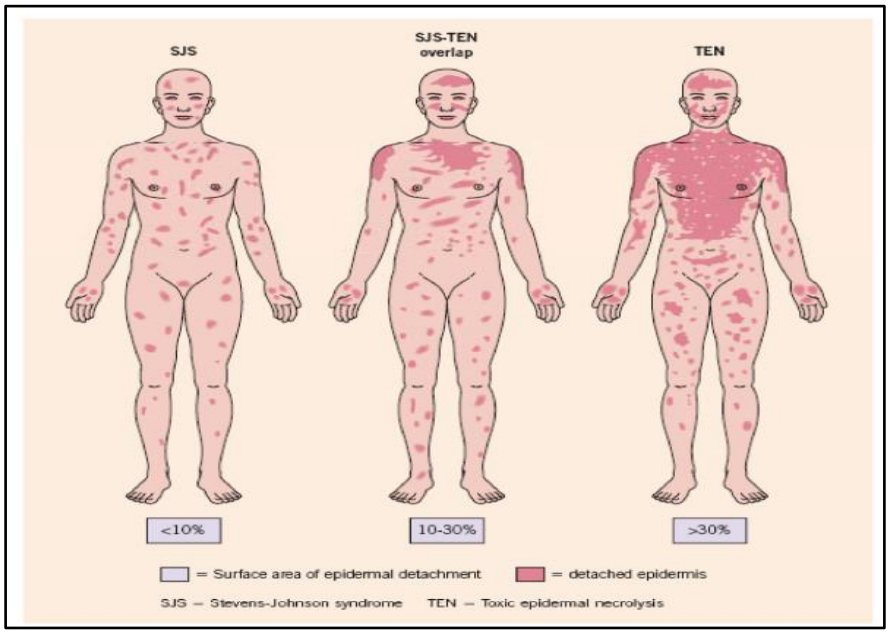


Figure 1.

Table 1: Classification of bullous erythema multiforme and epidermal necrolysis as proposed by Bastuji-Garin *et al.*

Classification	Type of lesions	Distribution	Percentage of BSA detached/ detachable
Bullous EM	Typical targets	Acral	-
SJS	Spots ± atypical targets	Generalized	<10
Overlap SJS-TEN	Spots ± atypical targets	Generalized	≥10-<30
TEN with spots	Spots ± atypical targets	Generalized	≥30
TEN without spots	Diffuse erythema, no spot or target	Generalized	≥10

SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, EM: Erythema multiforme, BSA: Body surface area

**Reference 77*

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[12]. Incidence is

estimated at 2-3 cases/million population/year in Europe[13].It is much more common in individuals with HIV(Estimated 1-2/1,000 in Canada)[14].It is more common in female than males[15].Most patients are aged 10-30 but cases have been reported in children as young as 3 months.

ETIOLOGY:

Various etiologic factors have been implicated as causes of Stevens-Johnson syndrome. Drugs most commonly are blamed. The 4 etiologic categories are as follows:

- Infectious
- Drug-induced
- Malignancy-related
- Idiopathic

Infectious Causes

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 pneumonia[16,17]
- Rickettsial infections
- Tularemia
- Typhoid

Drug Induced

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[18].

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[19]. Antiretroviral drugs implicated in Stevens-Johnson syndrome include nevirapine and possibly other non-nucleoside reverse transcriptase inhibitors[20].

Stevens-Johnson syndrome has also been reported in patients taking the following drugs:

- Modafinil (Provigil)
- Allopurinol[21]
- Mirtazapine[22]
- TNF-alpha antagonists (eg, infliximab, etanercept, adalimumab)[23]
- Cocaine
- Sertraline
- Pantoprazole
- Tramadol

Genetic Factors:
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-DR7
- HLA-A2
- HLA-B*5801
- HLA-A*0206
- HLA-DQB1*0601

Certain of these HLA alleles are associated with an increased probability of developing Stevens-Johnson syndrome upon exposure to specific drugs. HLA-B*5801 confers a risk of allopurinol-related reactions[24]. Pretreatment screening is not readily available[25]. Whites with HLA-B*44 appear to be more susceptible to develop Stevens-Johnson syndrome. HLA-A29, HLA-B12, and HLA-DR7 are frequently associated with sulfonamide-induced Stevens-Johnson syndrome, while HLA-A2 and HLA-B12 are often encountered in Stevens-Johnson syndrome induced by nonsteroidal anti-inflammatory drugs (NSAIDs). HLA-A*0206 and HLA-DQB1*0601 allele have been shown to be was strongly associated with Stevens-Johnson syndrome with ocular disease[26,27]. Nevertheless, whether the presence of those genes constitutes a predisposition to Stevens-Johnson syndrome or whether those genes are in linkage disequilibrium with more relevant adjacent genes is unknown[28].

SIGNS AND SYMPTOMS:
Typical prodromal symptoms of Stevens-Johnson syndrome are as follows:

- Cough productive of a thick, purulent sputum
- Headache
- Malaise
- Arthralgia

Patients may complain of a burning rash that begins symmetrically on the face and the upper part of the torso. The cutaneous lesions are characterized as follows:

- The rash can begin as macules that develop into papules, vesicles, bullae, urticarial plaques, or confluent erythema
- The typical lesion has the appearance of a target; this is considered pathognomonic
- In contrast to the typical lesions of erythema multiforme, these lesions have only 2 zones of color
- The lesion's core may be vesicular, purpuric, or necrotic; that zone is surrounded by macular erythema
- Lesions may become bullous and later rupture, leaving denuded skin; the skin becomes susceptible to secondary infection
- Urticarial lesions typically are not pruritic
- Infection may be responsible for the scarring associated with morbidity
- Although lesions may occur anywhere, the palms, soles, dorsum of the hands, and extensor surfaces are most commonly affected
- The rash may be confined to any one area of the body, most often the trunk

Signs of mucosal involvement can include the following:

- Erythema
- Edema
- Sloughing
- Blistering
- Ulceration
- Necrosis

The following ocular signs may be noted on slit-lamp examination:

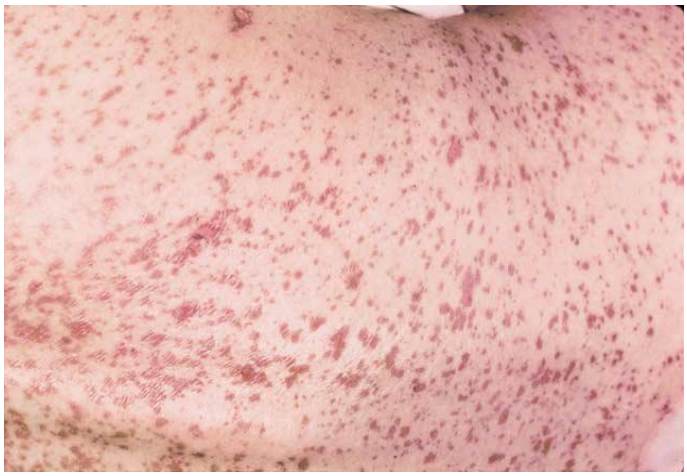
- Eyelids: Trichiasis, distichiasis, meibomian gland dysfunction, blepharitis
- Conjunctiva: Papillae, follicles, keratinization, subepithelial fibrosis, conjunctival shrinkage, foreshortening of fornices, symblepharon, ankyloblepharon

- Cornea: Superficial punctate keratitis, epithelial defect, stromal ulcer, neovascularization, keratinization, limbitis, conjunctivalization, stromal opacity, perforation.

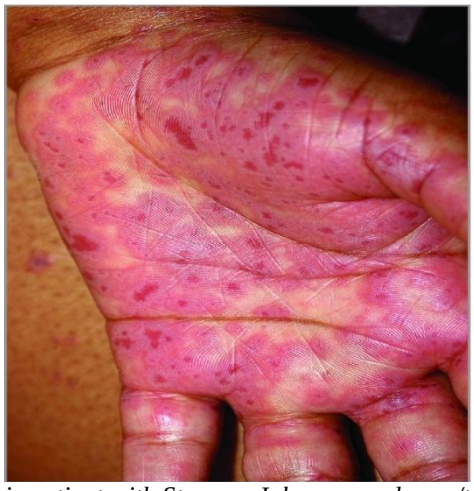
The typical clinical course of SJS begins within 8 weeks (usually 4 to 30 days) following the first exposure to the causative agent. Only in very rare cases where an inadvertent rechallenge occurs do symptoms appear within hours. Patients who develop SJS/TEN can have varying levels of cutaneous, extracutaneous, and mucous membrane manifestations (Table 2)[67].

Table2. Clinical Signs and Symptoms of SJS

Cutaneous	Mucous Membrane[a]	Extracutaneous
Initial phase: • Erythematous, dusky red, flat, atypical targetoid macules • Lesions symmetrically distributed on the face/trunk/proximal part of limbs but can spread to entire body *Later phase:* • Lesions progressively coalesce and evolve into flaccid blisters • Epidermal detachment	• *Ocular:* eyelid edema, redness, photophobia, discharge, lacrimation • *Buccal:* erosive hemorrhagic lesions, grayish-white pseudomembranes and crust on lips • *Genital:* erosive hemorrhagic lesions, painful urination	• *Nonspecific:* fever, pain, weakness • *Respiratory*[b]*:* respiratory distress • *Gastrointestinal*[b]*:* diarrhea, nausea, malabsorption, colonic perforation, melena • *Renal*[b]*:* proteinuria, hematuria, microalbuminuria



Typical Pattern of Stevens–Johnson Syndrome.
Blisters develop on widespread purpuric macules.



Atypical targets. On the palm of this patient with Stevens–Johnson syndrome/toxic epidermal necrolysis there are numerous circular lesions; most are characterized by a dark red centre surrounded by a pink ring. In some areas, the lesions are confluent.

PATHOPHYSIOLOGY:

The pathogenesis of SJS is not fully understood but is believed to be immune-mediated, as re-challenging an individual with the same drug can result in rapid recurrence of SJS[37,38].

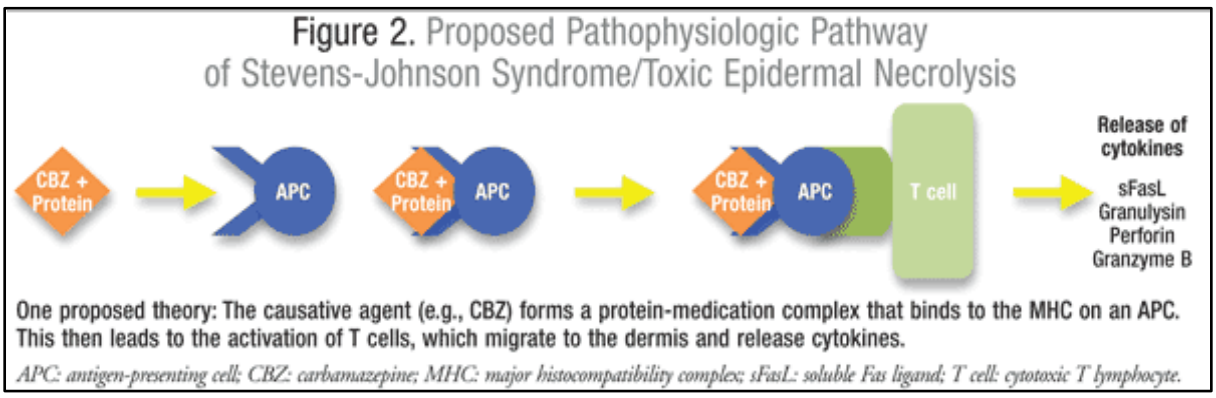
An idiosyncratic, delayed hypersensitivity reaction has been implicated in the pathophysiology of Stevens-Johnson syndrome. Certain population groups appear more susceptible to develop Stevens-Johnson syndrome than the general population. Slow acetylators, patients who are immunocompromised (especially those infected with HIV)[39,40], and patients with brain tumors undergoing radiotherapy with concomitant antiepileptics are among those at most risk. Slow acetylators are people whose liver cannot completely detoxify reactive drug metabolites. These drug metabolites may have direct toxic effects or may act as haptens that interact with host tissues, rendering them antigenic.[41,42]

Antigen presentation and production of tumor necrosis factor (TNF)–alpha by the local tissue dendrocytes results in the recruitment and augmentation of T-lymphocyte proliferation and enhances the cytotoxicity of the other immune effector cells[43].A "killer effector molecule" has been identified that may play a role in the activation of cytotoxic lymphocytes[44].The activated CD8+ lymphocytes, in turn, can induce epidermal cell apoptosis via several mechanisms, which include the release of granzyme B and perforin.

It has been postulated that SJS can occur as a delayed hypersensitivity or cell mediated immune reactions inresponse to certain drugs or their metabolites or infectious organisms. The people with genetic predisposition toa drug hypersensitivity reaction, immunocompromised are at increased risk of SJS[29,45].The exact mechanism involved in pathogenesis of SJS has been extensively studied by various authors andmany theories have been proposed by them. Here we highlight the two mechanisms that were assumed to beinvolved in pathogenesis.The ultimate effect of SJS is detachment of epidermis from the dermis due to the apoptosis of thekeratinocytes that are present at the epidermal-dermal junction.

These various theories focus on how theapoptosis of keratinocyte is carried out.According to some hypothesis, this keratinocytes apoptosis has been carried out by the activation ofcytotoxic T- lymphocytes in response to the antigens like drugs, infectious organisms etc[46]. first the Ag is upregulating the cell adhesion molecules that promotes the accumulation of leukocytes. Then the engulfed Ag are presented to T cells that were activated and become cytotoxic to keratinocytes. In turn the activatedmacrophages will release the IL and other lymphocytes. All these together lead to the keratinocytes apoptosis ornecrosis.Additionally, some researches has been focused on vitamin A toxicity as the mainstay of development of SJS.According to these studies it has been postulated that the antigens either the drug or the others will damage theliver, the organ that is responsible for the storage of Vit-A. this results in Vit-A toxicity due to increased levelsof free Vit-A in the blood circulation. These free Vit-A will eventually activate the cytotoxic T- lymphocyteswhich is responsible for production of a molecule called granulysin. This granulysin along with Vit- A lead tonecrosis or apoptosis of keratinocytes[47].

The development of the cutaneous lesions and epidermal necrosis are thought to occur as a result of massive apoptosis of keratinocytes.This is suspected to be a cell-mediated cytotoxic reaction.Studies have confirmed the presence of various cytotoxic cells,including natural killer cells (NK) and drug-specific CD8+ T lymphocytes, within early cutaneous lesions.These cytotoxic cells are thought to lead to the amplification and release of cytokines, such as granulysin, perforin, and granzyme B, which likely play a separate role in apoptosis (Figure 2)[68].



DIAGNOSIS:

The diagnosis of SJS is done considering the clinical symptoms and the histopathology study. The main stay of the diagnosis of SJS depends on ruling out other diseases (differential diagnosis) that comes under same spectrum. The clinical symptoms that are considered to confirm the diagnosis are areas of erythematous and macules on skin that shows Nikolsky sky sign upon the mechanical pressure. Epidermal detachment with in

few minutes to hours of nikolsky appearance is characterised by development of blisters[48,49]. These clinical symptoms may also be observed in other diseases hence differential diagnosis helps in ruling out other diseases which is discussed in later section.

Histological observations in SJS include the following:

- Epidermal necrosis that is reflected by the presence of immediate cryosections or conventional
- formalin fixed sections of skin confirms the SJS.
- Keratinocyte necrosis appear as wide spread or dissemination or full thickness of necrosis.
- Sub-epidermal necrosis blistering is found in basal membrane zone.
- Lymphocytic infiltrate seen in upper epidermis either superficially or peri-vascularly.
- No deposition of Ig in epidermis-dermal zone[29].

Both SJS and TEN were same histopathologically.

DIFFERENTIAL DIAGNOSIS:

Major differential diagnosis of SJS are:

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

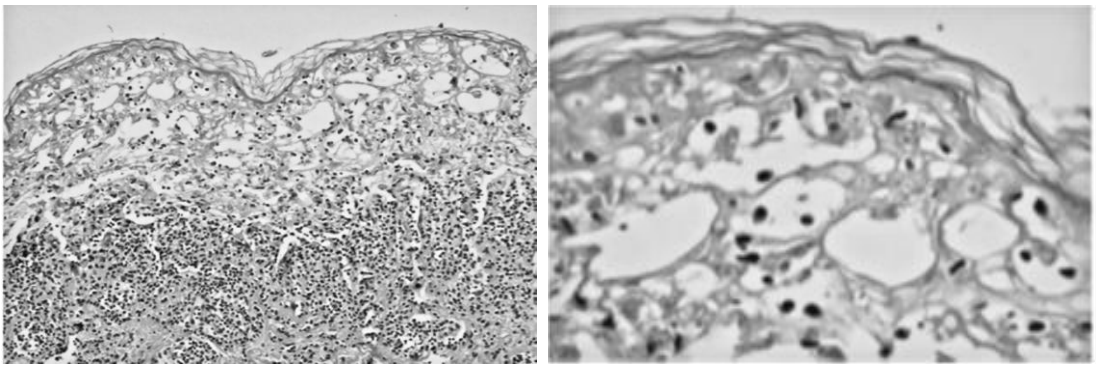
Differential diagnosis helps in ruling out all other diseases that look like similar in one way or the other. Clinically SJS should be differentiated from the diseases like blistering diseases, EM, Staphylococcus scaled skin syndrome, GBFDE.

Direct immune flouroscent staining helps in ruling out blistering diseases as there should be no Ig or othercomplement deposition in either epidermis or epidermal-dermal junction in SJS as the deposition is seen in blistering diseases. Varying amount of eosinophil was observed in tissue biopsy infiltrate of patients of SJS, EM and SJS/TEN. Other observations like less epidermal necrosis, more dermal inflammation and more exocytosis in EM observed compared to SJS. At this note the results of biopsies varies with the time of biopsy, onset of disease and from which part of the biopsy taken. Histopathological study of biopsies taken from lesions can distinguish SJS/TEN from other diseases but not from EM as they show the similar results in biopsies.

In early stages of disease maculopapular eruptions may present with or without oral lesions and conjunctivitis. These lesions were hemorrhagic and erosive in SJS but not in EM[32]. In contrast these EMM atypical forms with target lesions appear as wide disseminated with well demarcation and not confluent in children when compared to adult patients which makes diagnosis difficult in those patients[32,50]. In later stages where the epidermal detachment and blisters were well seen histologically information on the layer of epidermal detachment helps indifferentiate the disease from staphylococcal scaled-kin syndrome. Even though macules and target lesions were not seen and mucosal involvement seen rarely in Staphylococcal scaled-skin syndrome, differential diagnosis should always be based on histopathological studies only[32,51].

In Generalised bullous fixed drug eruptions (GBFDE) characterised by well defined, oval/round plaques in brownish or voilaceous and blisters appearing on these plaques frequently similar to SJS but the BSA involved rarely exceeds 10% through which it is differentiated. The other features hat differentiates GBFDE from SJS are less intense of fever, malaise and far better prognosis. But the histopathological observations of both SJS and GBFDE show blisters superficially along with necrosis. Hence the differentiation of SKJS from GBFD shouldbe made clinically rather than histopathologically[32].

Skin peeling by the shedding of membrane observed in diseases like erythoderma or dermatitis is often confused as epidermal detachment seen in SJS clinically[32].



Pathological examination of the skin of a patient with Stevens-Johnson syndrome

Table 2: Differential diagnosis of Stevens-Johnson syndrome/toxic epidermal necrolysis

Disorder	Context	Dermatological features	Pathology	Etiology
Staphylococcal scalded skin syndrome	Infants	No mucous membrane involvement, perioral and flexural involvement, Nikolsky's sign in involved and apparently normal skin	Subcorneal detachment	Staphylococcus toxins
Acute generalized exanthematous pustulosis	Recent drug intake	Pustules	Subcorneal pustules	Medications
Generalized bullous drug fixed drug eruption	Older children	Well demarcated large blisters with absent or mild mucosal involvement	Often indistinguishable from TEN	Medications
Paraneoplastic pemphigus	Lymphoma	Severe mouth lesions, slower progression	Acantholysis, positive findings in direct immunofluorescence study	Autoimmunity
Acute graft versus host reaction	Bone marrow transplantation	Slower progression, liver and gut involvement	Very similar to TEN	Alloimmunity
Linear IgA bullous disease	Drug intake	Tense blisters	Subepidermal blister, positive findings in direct immunofluorescence study	Medications
BSLE	Features of SLE	Photodistribution, slower progression	Subepidermal blister, positive findings in direct immunofluorescence study	Autoimmunity

BSLE - Bullous SLE; SLE - Systemic lupus erythematosus; TEN - Toxic epidermal necrolysis; IgA - Immunoglobulin A

Table 4: Factors affecting prognosis in Stevens–Johnson syndrome/toxic epidermal necrolysis (noted by this expert group in clinical practice)

Parameter	Remarks
Age	Elderly age is a high-risk category as there is a high risk of complications, higher incidence of comorbidities and delayed wound healing
Sex	No difference in outcomes was noted between the two sexes
Pre- or co-existing diseases	Diabetes (poorly controlled or uncontrolled), HIV, SLE, oncologic disease. Compromised cardiac, renal, hepatic, hematologic, gastrointestinal, pulmonary, neurologic or vascular systems
Metabolic parameters	Hypoglycemia, hyperglycemia, hyponatremia, hypo- and hyper-kalemia, hypomagnesemia are key metabolic disturbances that could aggravate the disease condition
Sepsis	Onset of sepsis in already compromised denuded skin is a poor prognostic sign. Several factors contribute to this: altered immunologic events, altered drug and metabolic profile and altered hemodynamic profile
Nosocomial infections	Catheter-associated urinary tract infection, central line-associated blood stream infections and ventilator-associated pneumonia are common in SJS-TEN patients due to prolonged use of invasive lines
Extent of involvement	Risk of morbidity and mortality is directly proportional to
Denudation of skin (TEN)/purpuric or hemorrhagic necrosis (SJS)	The percentage of skin involved
Mucosal damage (oral, genital, nasal, ocular and anal)	The type, severity and number of mucosae involved
Time of reporting/detection of drug-related illness	Earlier detection of causative drug and its withdrawal improves prognosis
	Delayed detection increases the risk of complications arising from complications of immunosuppressive drugs, opportunistic infections, and compromised systemic functioning

SJS: Stevens–Johnson syndrome, TEN: Toxic epidermal necrolysis, SLE: Systemic lupus erythematosus, HIV: Human immunodeficiency virus

**Reference 77*

TREATMENT:

Management of patients with Stevens-Johnson syndrome is usually provided in intensive care units or burn centers. No specific treatment of Stevens-Johnson syndrome is noted; therefore, most patients are treated symptomatically. In principle, the symptomatic treatment of patients with Stevens-Johnson syndrome does not differ from the treatment of patients with intensive burns. Patients should be treated with special attention to airway and homodynamic stability, fluid status, wound/burn care, and pain control.

As soon as the diagnosis of SJS has been confirmed, the appropriate treatment modalities depend on the severity and prognosis of disease. A validated SCROTEN disease severity scoring system may be used to assess the progress in patients and based on this score the treatment can be addressed. Patient with a SCORTEN score 3 or above indicates increase in severity and hence the intensive care should be taken and treatment considering infections and other complications should be recommended[51].

Table 5. SCORTEN

Prognostic factors	Points	SCORTEN	Mortality rates (%)
Ag e >40 (years)	1	0-1	3.2
Heart rate >120/ms	1	2	12.1
Cancer or hematological malignancy	1	3	35.8
>10% body surface area	1	4	58.3
Serum urea >10 mmol/L	1	>5	90
Bicarbonate <20 mmol/L	1		
Serum glucose >14 mmol/L	1		

SCORTEN - Score of toxic epidermal necrolysis

WITHDRAWAL OF CAUSATIVE DRUG:

The causative drug is identified as underlying disease then withdrawal of the drug should be done. Predicting the drug as cause it should be based on the time when blisters or erosions appear, as if it occurs during the course of treatment with the respective drug. Some studies reveal that earlier the causative drug withdrawn, better the prognosis be[29,52]. If the drug causing the disease is with longer half-lives then such patients are at increased risk of fatality[52]. Some elements that should be considered to confirm the drug as the cause are time of drug administration of drug and the reports that support the drug can able to cause the SJS.

SUPPORTIVE CARE:

A critical element of supportive care is the management of fluid and electrolyte requirements. Intravenous fluid should be given to maintain urine output of 50 - 80 mL per hour with 0.5% NaCl supplemented with 20 mEq of KCl. Appropriate early and aggressive replacement therapy is required in case of hyponatraemia, hypokalaemia or hypophosphataemia which quite frequently occur. Wounds should be treated conservatively, without skin debridement which is often performed in burn units, as blistered skin acts as a natural biological dressing which likely favors re-epithelialization. Non-adhesive wound dressings are used where required, and topical sulfa containing medications should be avoided[50].

Table 6: Components of supportive care in toxic epidermal necrolysis/systemic lupus erythematosus

Component	Parameter	Remark
Environmental temperature	30-32°C	To prevent hypercatabolic state
Monitoring	Pulse rate, blood pressure, respiratory rate, body temperature Fluid intake and urine output chart Blood glucose Serum electrolytes Serum creatinine Blood culture Specific cultures* D-dimer assay* FDP*	To watch for progression to complications such as DIC, sepsis, renal failure, ARDS and MODS
Prevention of infection	Barrier nursing Minimal handling and regular changing of catheters Monitor for foci of sepsis, features of septicemia and DIC	Helps to reduce the chances of sepsis

*To be used where resources are available. FDP: Fibrin degradation products, DIC: Disseminated intravascular coagulation, MODS: Multiple organ dysfunction syndrome, ARDS: Acute respiratory distress syndrome

Reference 77

DRUG THERAPY:

Systemic steroids:

A recent retrospective monocenter study suggests that a short course "pulse" of high dose corticosteroids (dexamethasone) may be of benefit[53].Traditionally, systemic corticosteroids have remained the mainstay of therapy of Stevens-Johnson syndrome and toxic epidermal necrolysis in most centers. The rationale is that both these consitions are immune-mediated processes and corticosteroids suppress the intensity of the reaction, prevent/decrease the necrolysis of skin, reduce fever and discomfort and prevent damage to internal organs when given at an early stage and in sufficiently high dosage[77].

Evidence for the use of steroids:

The largest study to evaluate the effect of treatments, including steroids, was performed by Schneck et al. 34 The authors examined data from a case–control study that evaluated the risk factors for Stevens-Johnson syndrome or toxic epidermal necrolysis in six countries in Europe in a cohort of 379 patients with confirmed disease. The authors concluded that there was inadequate evidence that any specific treatment is established as effective with only corticosteroids showing a trend for possible benefit. They called for "a prospective randomized trial to be conducted before any conclusions can be drawn, recommending that corticosteroids be trialled first." A recently published review identified six retrospective studies which analyzed the role of steroids in the survival of patients with SJS/TEN[77].

Table 7: Summary of corticosteroid studies in Stevens-Johnson syndrome/toxic epidermal necrolysis

Author, year	Type of study	Patients receiving corticosteroids	Dose of corticosteroids	Mortality	Level of evidence	Remarks
Schulz *et al.*, 2000[36]	Retrospective non-controlled case series	TEN (34)	Not clearly mentioned	13/34	II	Steroid exposure not associated with an increase in mortality
Tripathi *et al.*, 2000[44]	Retrospective non-controlled case series	SJS (67)	Methylprednisolone 160-240 mg daily; tapered when clinical response seen (no mean duration given)	1/67 (mortality was unrelated to SJS)	II	All patients had a favorable outcome and there was no mortality or permanent sequelae related to SJS
Kim *et al.*, 2005[37]	Retrospective non-controlled case series	TEN (21)	Methylprednisolone 250-1000 mg daily, later switched to oral prednisolone	6/21	III	The authors concluded that the low mortality rate compared with previous studies may be a result of the high rates of steroid use and therefore, suggested that steroid therapy should be used early
Kardaun and Jonkman, 2007[46]	Retrospective non-controlled case series	SJS (1), SJS-TEN overlap (4), TEN (7)	First four patients: IV dexamethasone 100 mg once daily for 3 days+500 mg cyclophosphamide Subsequent patients: 1.5 mg/kg IV dexamethasone for 3 days	1/12	III	Authors concluded that short-term dexamethasone pulse therapy, given at an early stage of the disease may contribute to a reduced mortality rate in SJS/TEN without increasing healing time
Schneck *et al.*, 2008[34]	Retrospective multicenter non-controlled case series	SJS (57), SJS-TEN overlap (44), TEN (18)	Maximum steroid dose 250 mg prednisolone equivalent given for a median of 4 days (2-12 days)	21/119	II	The authors concluded that there was inadequate evidence that any specific treatment is established as effective for patients with SJS or TEN with only corticosteroids showing a trend for possible benefit
Hirahara *et al.*, 2013[48]	Retrospective non-controlled case series	SJS (3), SJS-TEN overlap (2), TEN (3)	1000 mg IV methylprednisolone for 3 days	0/8	III	There was no mortality in spite of the SCORTEN-predicted mortality being 1.6. A decrease in proinflammatory cytokines was also noted
Pasricha *et al.*, 1996[50]	Retrospective non-controlled case series	TEN (5)	IV dexamethasone 16-24 mg/day, tapered and withdrawn within 7-10 days	0/5	III	Authors concluded that corticosteroids used in appropriate doses ensure early recovery
Das *et al.*, 2013[54]	Prospective, non-controlled case series	TEN (18)	Injection dexamethasone (1 mg/kg/day till erythema subsided) tapered and withdrawn within 5 days after subsidence of erythema	0/18	II	Two other patients were given (IVIG) in a total dose of 2 g/kg (0.4 g/kg/day for 5 consecutive days), both of whom survived. Authors opined that systemic corticosteroids in the initial phase of TEN are life-saving drugs
Rai and Srinivas 2008[55]	Retrospective non-controlled case series	TEN (3)	Injection dexamethasone 100 mg for 2 days (2 patients) or 4 days (1 patient) followed by cyclosporine 2 mg/kg/day (tapered 50 mg every 3rd day and stopped after 2 weeks)	0/3	III	Authors concluded that the combination of initial high dose of steroids and subsequent cyclosporine is a safe alternative

SCORTEN: Severity-of-illness score for toxic epidermal necrolysis, SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, IVIG: Intravenous immunoglobulin, IV: Intravenous

**Reference 77*

High-dose intravenous immunoglobulin's:

As a consequence of the discovery of the anti-Fas potential of pooled human intravenous immunoglobulins (IVIG) in vitro[54], IVIG have been tested for the treatment of TEN, and their effect reported in different non-controlled studies. To date, numerous case reports and 12 non-controlled clinical studies containing 10 or more patients have analyzed the therapeutic effect of IVIG in TEN. All except one study[55] confirm the known excellent tolerability and a low toxic potential of IVIG when used with appropriate precaution in patients with potential risk factors (renal insufficiency, cardiac insufficiency, IgA deficiency, thrombo-embolic risk)[56]. The concomitant administration of corticosteroids or immunosuppressive agents remains controversial. IVIG has also been applied in a few children with SJS/TEN, and two non-controlled studies suggest a possible benefit[57,58].

Table 9: Summary of intravenous immunoglobulin studies in Stevens–Johnson syndrome/toxic epidermal necrolysis

Authors, year	Study design	Number of patients	Dose of IVIG/regimen	Mortality (%)	Level of evidence	Remarks
Viard *et al.*, 1998[69]	Multiple centers; prospective; case series; non-controlled	TEN (10)	0.2-0.75 g/kg daily for 4 days	0/10 (0)	III	Effective variable IVIG dosing
Stella *et al.*, 2001[72]	Single burns unit Prospective; case series; non-controlled	SJS (1) Overlap SJS-TEN (7) TEN (1)	0.6-0.7 g/kg daily for 4 days	1/9 (11.1)	III	Effective
Bachot *et al.*, 200376	Single dermatology HDU; prospective; case series; with SCORTEN-predicted mortality as comparator	SJS (9) SJS-TEN Overlap (5) TEN (20)	2 g/kg given over 2 days	11/34 (32.4) as compared to SCORTEN-predicted mortality 8.2/34 (23)	II	Ineffective
Prins *et al.*, 2003[69]	Multiple centers; retrospective; case series (including previously reported cases, from three other studies); non-controlled	Overlap SJS/TEN (7) TEN (41)	Mean 0.7 g/kg daily for 4 days	6/48 (12.5)	II	Effective
Trent *et al.*, 2003[70]	Single dermatology unit; retrospective; case series with SCORTEN-predicted mortality as comparator	SJS-TEN Overlap (6) TEN (10)	1 g/kg daily for 4 days (n=15) 0.4 g/kg daily for 4 days (n=1)	1/16 (6.3) as compared to SCORTEN-predicted mortality 5.8/16 (36.3)	II	Effective
Al-Mutairi *et al.*, 2004[73]	Single dermatology unit retrospective, non-controlled	TEN (12)	0.5-1.0 g/kg for 4-5 days	0/11 (0)	III	Effective
Brown *et al.*, 2004[74]	Single burns unit; retrospective; case-control	TEN (24)	0.4 g/kg for 4 days	10/24 (41.7) as compared to 6/21 (28.6) mortality in controls	II	Ineffective
Shortt *et al.*, 2004[75]	Single burns unit; retrospective; case-control	SJS-TEN Overlap (16)	Mean dose 0.7±0.2 g/kg Daily for 4±1 days	4/16 (25) as compared to 6/16 (37.5) mortality in historic controls	III	Equivocal
Kim *et al.*, 2005[37]	Dermatology unit; retrospective; case series with SCORTEN-predicted mortality as comparator	TEN (14)	IVIG: 1.6-2.0 g/kg	1/14 (7.1) as compared to SCORTEN-predicted mortality: 2.4/14 (17.1)	III	Effective

IVIG: Intravenous immunoglobulin, SCORTEN: Severity-of-illness score for toxic epidermal necrolysis, SJS: Stevens–Johnson syndrome, TEN: Toxic epidermal necrolysis, HDU: High dependency unit

*Reference 77

Ciclosporin (CsA):

Patients treated with CsA had significantly shorter time to complete re-epithelialisation, and fewer patients with multi-organ failure and death were observed[59]. A small case series with three TEN patients treated initially with high-doses of intravenous dexamethasone followed by CsA showed a stop in disease progression within 72 hrs[60]. Other single case reports also reported a positive effect of the use of CsA in TEN[61,62]. Recently, Valeyrie-Allanore L conducted an open, phase II trial to determine the safety and possible benefit of ciclosporin[63].

Table 8: Summary of cyclosporine studies in Stevens-Johnson syndrome/toxic epidermal necrolysis

Authors, year	Type of study	Number of patients	Dose of cyclosporine	Mortality	Level of evidence	Remarks
Arévalo *et al.*, 2000[59]	Retrospective, non-controlled case series	17 patients of TEN (11 patients CsA, 6 patients with cyclophosphamide and steroid)	3 mg/kg/day orally every 12 h for 2 weeks and then tapered off (10 mg a day reduction every 48 h)	0/11 (CsA group) as compared to 3/6 (steroids + cyclophosphamide group)	II	Authors concluded that immunosuppressive treatment with CsA is safe and is associated with a rapid re-epithelialization rate and a low mortality rate in patients with severe TEN
Valeyrie-Allanore *et al.*, 2010[66]	Retrospective, non-controlled case series	SJS (10), SJS/TEN overlap (12) and TEN (7)	1.5 mg/kg BD 1 mg/kg BD and 0.5 mg/kg BD for 10 days each in a tapering fashion	0/29 (as compared to 2.8 deaths predicted by SCORTEN)	II	Both the death rate and the progression of detachment were lower than expected, suggesting usefulness of cyclosporin in SJS and TEN
Singh *et al.*, 2013[64]	Retrospective, non-controlled case series	11 patients CsA, 9 corticosteroids	3 mg/kg/day for 7 days, then 2 mg/kg/day for 7 days	0/11 (as compared to 1.1 deaths predicted by SCORTEN)	II	Authors concluded that cyclosporine has an encouraging role in the management of SJS and TEN
Kirchhof *et al.*, 2014[67]	Retrospective, single-center, non-controlled case series	64 patients (28 SJS, 19 SJS/TEN overlap and 17 TEN); 12 received only supportive treatment, 35 received IVIG, 15 CsA and 2 both	CsA 3-5 mg/kg/day for an average of 7 days. IVIG 1 g/kg/day for 3 days	The observed morality was 29.7% (n=11) for IVIG and 5.9% (n=1) for cyclosporine-treated patients	II	The use of cyclosporine over IVIG may offer a greater mortality benefit in the treatment of SJS/TEN, the study suggested a potential therapeutic benefit of cyclosporine use in the treatment of SJS/TEN and questioned the purported benefits of IVIG

CsA: Cyclosporine A, SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, IVIG: Intravenous immunoglobulin, SCORTEN: Severity-of-illness score for toxic epidermal necrolysis

*Reference 77

Treatment for ocular manifestations:

Treatment of acute ocular manifestations usually begins with aggressive lubrication of the ocular surface. As inflammation and cicatricial changes ensue, most ophthalmologists use topical steroids, antibiotics, and symblepharon lysis. In case of exposure keratopathy, tarsorrhaphy may be required. Maintenance of ocular integrity can be achieved through the use of amniotic membrane grafting, adhesive glues, lamellar grafts, and penetrating keratoplasty, either in the acute phase or in subsequent follow-up care. Visual rehabilitation in patients with visual impairment can be considered once the eye has been quiet for at least 3 months.

Topical treatment:

Although the blisters are fragile, they should be left in place or only be punctured. Erosions can be treated with chlorhexidine, octenisept or polyhexanide solutions and impregnated nonadhesive mesh gauze. The latter is important if environmental factors, such as high room temperature or alternating pressure mattress, lead to skin dryness. Silver sulfadiazine should be avoided, at least if the causative drug was cotrimoxazole or another anti-infective sulfonamide. Some burn care specialists debride the skin under general anesthesia and apply allografts or other types of coverage. However, this rather aggressive procedure is not tolerated well by many elderly patients with underlying diseases[64]. Furthermore, hypertrophic scars may occur if debridement is carried out extensively and if allografts are fixed with staples directly into the skin.

For affected mucosal surfaces, specialized care is critical. The severity of the mucosal involvement is often not in line with the amount of skin detachment and overlooked mucosal lesions can lead to life-long problems. A multidisciplinary approach is needed and in case of urethral involvement urologists should be involved. Appropriately placed wet dressings or sitz baths may help to avoid adhesions or strictures of genital erosions in girls and women. Disinfectant mouth wash should be used to treat oral erosions and mild ointment, such as dexpanthenol, should be applied on erosions and bloody crusts of the lips. In the case of eye-involvement, regular ophthalmologic consultation is crucial. Specialized lid care is needed on a daily basis and anti-inflammatory eye drops should be given several times per day.Severe blepharitis may lead to entropion with trichiasis (in growing eye lashes) causing further corneal damage.

Various specialized approaches to ocular involvement have been suggested, such as stem cell generation of replacement cells, amniotic membrane transplantation and scleral lenses, but are not yet widely

accepted[65,66]. Nevertheless, experienced ophthalmologists should be involved in the care of all patients with SJS/TEN, even those that do not present with eye-involvement right away, since it may occur with some delay.

Table 9.Dosing Regimens in Published Case Reports

Drug	Dosing
Prednisolone	PO: 10-600 mg/day
Hydrocortisone	IV: 100-700 mg/day 10-15 mg/kg/day
Methylprednisolone	IV: 40-80 mg/day 600-1,000 mg/day 1-4 mg/kg/day
Dexamethasone	IV: 100 mg/day 1.5 mg/kg/day
IVIG	IV: 0.2-2 mg/kg/day x 3-4 days
Cyclosporine	IV or PO: 3-5 mg/kg/day

IVIG: intravenous immunoglobulin.

Stevens–Johnson syndromein pregnancy:

Steven Johnson syndrome in pregnancy puts two lives at risk and hence, it requires the immediate attention of both dermatologist and gynecologist. A large majority of patients who develop SJS in pregnancy are human immunodeficiency virus-positive and nevirapine is the most common drug incriminated[77].

Effect on mother

Pregnancy as such is not a risk factor for mortality in toxic epidermal necrolysis. A review of the literature by Struck et al. supports a high survival rate of both mother and child. Long-term complications of genital involvement in SJS/TEN include vaginal stenosis and adhesions, endometriosis and telangiectasia. To prevent vaginal complications, a vaginal mold with local corticosteroids/lubricant gel can be inserted in the vagina to prevent adhesions[78].

Effect on fetus

Maternal toxic epidermal necrolysis is known to cause fetal stress and preterm labor. Hence, it is prudent to keep a close watch on fetal parameters during management. In most cases, the child is not affected by toxic epidermal necrolysis. In fact, toxic epidermal necrolysis in neonates/early infancy is very rare and only some cases have been reported. Rodriguez et al. have reported a case of toxic epidermal necrolysis in both a mother and her stillborn child[79].

Management

Management of toxic epidermal necrolysis in pregnant women is not very different from that of non-pregnant patients. Systemic steroids should not be favored in the first trimester, but may be useful in the third trimester as they help to increase the lung maturity of fetus, more so in case of preterm labor. Intravenous immunoglobulin and cyclosporine (pregnancy category C) can also be used in individual cases[77,80]. Intravenous immunoglobulin has been used safely in treating pregnant patients with toxic epidermal necrolysis. There is not much literature on the use of cyclosporine in pregnant women with toxic epidermal necrolysis. The use of cyclosporine in pregnant renal transplant recipients has been associated with adverse effectsin newborns. However, these adverse effects are usually seen with long-term use of cyclosporine to prevent rejection and toxic epidermal necrolysis does not require long-term treatment.

Stevens–Johnson syndrome/toxic epidermal necrolysis in children

Stevens–Johnson syndrome/toxic epidermal necrolysisin children does not differ significantly in its etiology,clinical features and management strategies from adult SJS/TEN. Some points, however, are worth mentioning. Drugs are the most common culprits in SJS/TEN (both children and adults). However, the likelihood of infections (Mycoplasma and Cytomegalovirus) inducing SJS/TEN is relatively higher in children

as compared to adults.5,6 Sulphonamides, penicillins and nonsteroidal anti-inflammatory drugs are more commonly implicated in drug-induced pediatric SJS/ TEN owing to their more frequent use in children.

Anticonvulsants are another class of drugs commonlyimplicated in SJS/TEN in children. Stevens–Johnson syndrome and toxic epidermal necrolysis rarely cause mortality in children, but significant morbidity is seen.In a study of 21 patients by Prendiville et al., there was an excellent response to supportive care alone which included reverse barrier isolation, intravenous fluids and nutritional support, meticulous skin care, early detection and treatment of infection and daily ophthalmologic examination, with no mortality.30 It has been seen that the energy needs of children with SJS/TEN are 22% less than the age and wound size matched burn patients. The recommended equation for the estimation of energy requirements in children with SJS/TEN is: (24.6 × weight in kg) + (% wound × 4.1) + 940.

Corticosteroids, intravenous immunoglobulin and cyclosporine have been utilized for specific therapy of pediatric SJS/TEN in various studies. Kakourou et al. suggest a bolus infusion of methylprednisolone (4 mg/kg/day) for 3–7 days which showed a significant reduction of the period of fever and acute eruption and milder signs of prostration as compared to supportive therapy alone.47 No relapses occurred after treatment was discontinued. They concluded that an early and short course of intravenous corticosteroids favorably influenced the course of SJS/TEN in children. Intravenous immunoglobulin has been used as a treatment with mixed results. An Indian study by Mangla et al. evaluated the role of low-dose intravenous immunoglobulin (0.05–0.1 mg/kg/dayfor 5 days) in pediatric toxic epidermal necrolysis and found it to be a safe and effective treatment. Cyclosporine has also shown promising results in the treatment of pediatric SJS and TEN.

RISKFACTORS:

HIV

The incidence of SJS was found to be 100 times higher in individuals infected with HIV relative to the general population. The increased risk in this population is attributed to polypharmacy, immune dysregulation, and the presence of multiple concurrent infections. Medication Exposure Rapid introduction of high dosages of medications associated with SJS further increases a patient's risk of developing SJS[69].

HLA Subtypes

It has been discovered that specific HLA subtypes carry an increased risk for development of SJS in various populations after exposure to certain classes of medications. It has also been noted that specific HLA subtypes A*0206 and DQB1*0601 carry increased risk for ocular complications secondary to SJS[69].

COMPLICATIONS:

- Dehydration and acute malnutrition
- Shock and multiorgan failure
- Thromboembolism and disseminated intravascularcoagulation
- Gastrointestinal ulceration, necrolysis, strictures andperforation
- **Skin:** secondary infection and scarring
- Mucosal pseudomembrane formation may lead to
- mucosal scarring and loss of function of the involvedorgan system
- **Lung:** mucosal shedding in the tracheobronchial treemay lead to respiratory failure
- Eye complications include corneal ulceration andanterior uveitis. Sight impairment may developsecondary to severe keratitis or panophthalmitis in 3-10% of patients
- Vaginal stenosis and penile scarring have been reported
- Renal complications are uncommon but renal tubularnecrolysis and acute kidney injury may occur.

PREVENTION:

Keeping in mind, the significant morbidity and mortality associated with the disease; it would have been extremely beneficial if the disease per se could be prevented. Pharmacogenetic screening of HLA alleles before initiating a drug has already been shown useful in the prevention of cutaneous adverse drug reactions[71]. In December 2007, US Food and Drug Administration (USFDA) recommended HLA-B*1502 testing before the use of carbamazepine in the Asian population. Since then, HLA testing has been made mandatory in Hong Kong, Taiwan, and Singapore. However, there are many debatable points regarding this strategy. It is not clear

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whether to avoid phenytoin, oxcarbazepine, and lamotrigine in patients who test positive for HLA-B*1502[72]. Besides, the hypothesis of increased incidence of carbamazepine-induced SJS-TEN in HLA-B*1502 positivity does not hold true in a few parts of Korea and Japan[73].

Most importantly, in a country like ours; where financial constraints become the rate-limiting factor before executing any strategy; pharmacogenomic testing is not a practical option. In Hong Kong and Taiwan, the HLA-B*1502 tests are offered without any cost to patients. However, in Singapore, the tests are subsidized up to 25% in government hospitals the private patients pay for the test in full. Of note, there are reports of cases of carbamazepine-induced SJS-TEN in HLA-B*1502 negative patients[74]. Adding to the already existing problems, in near future, it is possible that Asian countries will face the problem of testing for HLA-B*5801 before prescription of allopurinol[75]. Since the patients with chronic kidney disease and those who test positive for HLA-B*5801 are at a significantly higher risk of allopurinol-induced SCAR; a question arises; whether the HLA testing should be made mandatory in Asia-Pacific regions in patients who can afford. Besides, USFDA recommends testing for HLA-B*5701 for patients receiving abacavir[76].

The following measures are important to prevent sepsis in patients with SJS/TEN.

- Barrier nursing and sterile handling of the patient
- Regular hand hygiene with chlorhexidine hand rubs and hand washes to be practiced by health‐ care workers and caregivers
- Avoid unnecessary insertion of urinary catheters, intravenous lines or central lines
- If used, urinary catheters, intravenous lines and central lines must be handled minimally and changed regularly
- Monitor for foci of sepsis in the body, features of septicemia and disseminated intravascular coagulation
- Environmental controls for dependency units (air exchanges, humidity and temperature control) and intensive care unit
- Activate sepsis protocols early
- Judicious use of antibiotics[77].

II. Conclusion

SJS is a rare, serious disorder of skin and mucous membranesusually requires hospitalization. It is usually a reaction to a medication or an infection. Treatment focuses on eliminating the underlying cause, controlling symptoms and minimizing complications. Recovery after SJS can take weeks to months, depending on the severity of condition.The pathogenesis of SJS/TEN has not been completely solved, but specific genetic predispositions, which vary among ethnic groups and differ between certain causing drugs, were identified. Since to date no treatment has been identified to stop the progression of skin detachment, supportive management is crucial to improve the patient's health condition, probably more than specific immunomodulation treatments. Despite all therapeutic efforts, death rate is high and increases with disease severity, patients age and underlying medical conditions. Survivors may suffer from long-term sequelae such as strictures of mucous membranes which includes severe eye problems.

ABBREVATIONS:

SJS	**:**	Stevens-Johnson syndrome
TEN	**:**	Toxic Epidermal Necrolysis
SCAR	**:**	Severe Cutaneous Adverse Reactions
AGEP	**:**	Acute Generalized Exanthematous Pustulosis
DRESS	**:**	Drug Reaction with Eosinophilia and Systemic Symptoms Complex
EMM	**:**	Erythema Multiforme Major
CBZ	**:**	Carbamazepine
HZ	**:**	Herpes Zoster
BSA	**:**	Body Surface Area
ADR	**:**	Adverse Drug Reaction
RUM	**:**	Rational Use Of Medicines
EAM	**:**	Adverse Event To Medicine
TNF-α	**:**	Tumor Necrosis Factor-α
NSAIDS	**:**	Nonsteroidal Anti-Inflammatory Drugs
GBFDE	**:**	Generalised Bullous Fixed Drug Eruptions
IVIG	**:**	Intravenous Immunoglobulins

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IOSR Journal of Pharmacy (IOSR-PHR) is UGC approved Journal with Sl. No. 3365, Journal No-62875

Gotte Priyanka. "A Review on Steven Johnsons Syndrome: Hypersensitivity Reaction". IOSR Journal of Pharmacy (IOSRPHR), vol. 9, no. 9, 2019, pp. 18-38.