

**Review Article****REVIEW ARTICLE ON STEVENS JOHNSON SYNDROME**

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Received 16 June 2017; Accepted 13 July 2017

ABSTRACT

Stevens-Johnson Syndrome (SJS) is rare, cutaneous, severe, drug-induced hypersensitivity reactions marked by widespread inflammation of the epidermis, ending in necrosis and the eventual sloughing of tissue. It is the syndrome associated with a rare, serious disorder of the skin, mucous membranes, genitals and eyes usually a reaction to a medication or an infection. There are drugs that have been linked to Stevens - Johnson syndrome, and these include some NSAIDs (non-steroid anti-inflammatory drugs), Allopurinol, Phenytoin, Carbamazepine, barbiturates, anticonvulsants, and sulfa antibiotics. The condition can sometimes attributed to a infection such as Mycoplasma, cytomegalovirus and in some cases there is no known cause for the onset of this Syndrome. Histopathological hallmark of this disease is widespread epidermal necrosis due to death by apoptosis of keratinocytes. The pathogenesis of SJS has not been completely solved, but specific genetic predispositions, which vary among ethnic groups and differ between certain causing drugs, were identified. A positive Nikolsky sign is helpful in the diagnosis of SJS. Drug provocation tests are contraindicated, since a subsequent exposure to the agent could trigger a new severe episode of SJS. Complete blood count (CBC) may show unspecific leukocytosis or even indicate superimposed secondary bacterial infection. Cultures of blood, urine and skin can reveal the agent of the underlying suspected infection. Skin biopsy is an additional final examination.

Complications include dehydration, sepsis, pneumonia, and multiple organ failure. Genetic research has identified several combinations of alleles and medications which when combined increase the risk of illness. Understanding pathophysiology is key for treating and limiting the destructive mechanism for disease. The success of treatment depends on early recognition of the condition, removal of the causative medications and intensive supportive care in a well-equipped hospital.

Keywords: Stevens Johnson syndrome, acetylators, Nikolskysign, Sepsis, Keratinocytes

Introduction

Stevens - Johnson syndrome (SJS) is rare, cutaneous, severe, drug-induced hypersensitivity reactions marked by widespread inflammation of the epidermis, ending in necrosis and the eventual sloughing of tissue. [1] It is the syndrome associated with a rare, serious disorder of the skin, mucous membranes, genitals and eyes usually a reaction to a medication or an infection.[2] Often, it begins with fever and flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters. The top layer of the affected skin dies, sheds and then heals.[1,2,3] It can also cause serious eye problems, such as severe conjunctivitis, iritis (an inflammation inside

the eye), corneal blisters and erosions and corneal holes. In some cases, the ocular complications from this condition can be disabling and lead to severe vision loss.[4] Mucous membranes, such as the mouth also typically involved. Complications include dehydration, sepsis, pneumonia,

and multiple organ failure.[5, 6] There are drugs that have been linked to Stevens - Johnson syndrome, and these include some NSAIDs (non-steroid anti-inflammatory drugs), Allopurinol, Phenytoin, Carbamazepine, barbiturates, anticonvulsants, and sulfa antibiotics. The condition can sometimes attributed to a infection such as Mycoplasma, cytomegalovirus and in some cases there is no known cause for the onset of

Stevens-Johnson Syndrome. However, the most common cause is through drug related reaction.[7,8]The syndrome was first described in 1922, when the American pediatricians Albert Mason Stevens and Frank Chambliss Johnson reported the cases of two young boys with skin eruptions of oval, dark red to purplish spots separated by normal tissue. The appearance looking like a bulls-eye. There was fever, conjunctivitis, inflamed mucus membranes, and one of the young boy had a total loss of vision. The pediatricians had never seen these conditions before and they had multiple consultants evaluate these patients. Their report was the first description of what later became Stevens-Johnson Syndrome.[12]SJS is life threatening conditions. The success of treatment depends on early recognition of the condition, removal of the causative medications and intensive supportive care in a well-equipped hospital. [5] Several agents with anti-inflammatory or immunosuppressive properties have been tried to alter the course of the disease but no single agent has their efficacy clearly proven by clinical trials.[8] Patients are treated in burn units. The first care should include supportive and symptomatic measures: body temperature control, hydration and electrolyte replacement, special attention to the airways, preventing secondary infection, pain control, maintenance of venous access distant from the affected areas, early oral nutrition or parenteral nutrition, if necessary anticoagulation. Skin lesions are treated according to the protocol for patients with large burns. Topical antiseptics can be used or just soap and water, in quick baths. Prophylactic antibiotic therapy is not recommended as it can induce resistance. [10]

PATHOPHYSIOLOGY

The pathophysiological mechanism is not fully understood. Some individuals have a genetic predisposition to develop such disorders: so-called slow acetylators, deficient in enzymes involved in the destruction of toxic drug metabolites, such as glutathione transferase. Recently, genetic association of some HLA major histocompatibility complex alleles with the occurrence of serious drug reactions has been described.[14]Histopathological hallmark of this disease is widespread epidermal necrosis due to death by apoptosis of keratinocytes.[11] Slow

acetylators, patients who are immunocompromised (especially those infected with HIV 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. Stevensjohnshonsyndrome is denoted by the widespread eruption of macules and papules which eventually lead to skin necrosis and sloughing and has been idiopathicillness.[9] Genetic research has identifiedseveral combinations of alleles and medications which whencombined, increase the risk of illness. The disease occurs when a drug metabolite damages the liver and the organ responsible for storage of Vitamin A, causing freeretinoidmolecules to spill into the circulation creating an acute, systemic Vitamin A toxicity.[10]Granulysin, a cytotoxic proteinproduced in massive quantities by both CD8+ T-Lymphocytes andnatural killer cells is the most prevalent molecule found in SJS blisters. Granulysin act as a cytokine for destructiveretinoid molecules (such as retinoic acid), combined together are responsible for keratinocyte apoptosis seen in SJS. As keratinocytes die off, the epidermis becomes detached from the dermis ending in tissue necrosis and sloughing.[10,11]Many classes of medications have been linked to SJS,including anticonvulsants, antibiotics, NSAIDS, corticosteroids and allopurinol. These medications increase circulating retinoid levels, either through hepatic release as a result of liver injury or through the inhibition of metabolism which leads to higher circulating retinol derivatives, such as retinoic acid, a powerful cell-lysingagent. Understanding pathophysiology is key for treating and limiting the destructive mechanism for disease. [9, 10, 11]

DIAGNOSIS

A positive Nikolsky sign is helpful in the diagnosis of SJS. The diagnosis relies on the one hand on clinical symptoms and on the other hand on histological features. Typical clinical signs initially include areas of erythematous and livid macules on the skin, on which a positive Nikolsky sign can be induced by mechanical pressure on the skin, followed within minutes to hours by the onset of epidermal detachment characterized by the

development of blisters.[13] Histological work up of immediate conventional formalin-fixed sections of the skin revealing wide spread necrotic epidermis involving all layers confirms the diagnosis.[15] In order to rule out autoimmune blistering diseases, direct immune fluorescence staining should be additionally performed. Drug provocation tests are contraindicated, since a subsequent exposure to the agent could trigger a new severe episode of SJS.[18] Complete blood count (CBC) may show unspecific leukocytosis or even indicate superimposed secondary bacterial infection. Cultures of blood, urine and skin can reveal the agent of the underlying suspected infection. Skin biopsy is an additional final examination and reveals necrosis in all layers of the epidermis caused by apoptosis of keratinocytes and epidermal detachment.[29] Serum levels of tumor necrosis factor-alpha and soluble IL-2, IL-6 and C-reactive protein receptors are typically elevated in patients with SJS.[27]

TREATMENT

Prompt withdrawal of culprit drug(s)

Prompt withdrawal of causative drugs should be a priority when blisters or erosions appear in the course of a drug eruption. Patients exposed to causative drugs with long half-lives have an increased risk of dying. In order to identify the culprit drug(s) it is important to consider the chronology of administration of the drug and the reported ability of the drug to induce SJS. The chronology of administration of a culprit drug between first administration and development of SJS is between 1 and 4 weeks in the majority of cases. [22]

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 without skin debridement which is often performed in burn units. Non-adhesive wound dressings are used where required, and topical

sulfa containing medications should be avoided. [23]

Treatment for ocular manifestations

Treatment of acute ocular manifestations usually begins with aggressive lubrication of the ocular surface. As inflammation and cicatricial changes occurs, most ophthalmologists use topical steroids, antibiotics, and symblepharonolysis. 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. 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. [4, 9]

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. 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. Furthermore, hypertrophic scars may occur if debridement is carried out extensively and if allografts are fixed with staples directly into the skin. 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. [25]

Drug therapy

Systemic steroids

A recent study suggests that a short course of high dose corticosteroids (dexamethasone) may be of

benefit. Some studies have also suggested the use of systemic corticosteroids in the early stage of SJS. Other studies failed to prove the effect of the agent and have demonstrated an increase in the chance of sepsis and other complications. Its use in SJS is still controversial but should not be recommended when extensive skin loss has already occurred.[20]

High-dose intravenous immunoglobulins

Theoretically it is best to give IVIG early (within 24-72 hours from first appearance of bullae) before Fas ligand and receptor binding has occurred, although it may still be effective if new bullae are still appearing. Sucrose-depleted IVIG is preferred since it has lower possibility of renal toxicity. Patient with IgA deficiency will develop anaphylaxis to IVIG. It is best to obtain a patient's IgA level before administering but awaiting the report might delay treatment. History of recurrent sinopulmonary infection and gastrointestinal infection may help to identify those with IgA deficiency which is very rare. It was based on in vitro demonstration that intravenous immunoglobulins can inhibit Fas-Fas ligand mediated apoptosis. [22]

Cyclosporin (CsA)

Patients treated with CsA had significantly shorter time to complete re-epithelialisation, and fewer patients with multi-organ failure and death were observed. Thus avoiding its side effects which commonly occur in long term use, this agent needs more comprehensive studies. [21]

COMPLICATIONS

Sepsis is the most important cause of mortality. Extensive erosions in patients are in risk of infection by bacteria and fungi which will result in pulmonary complications and multi-organ failure. Hyperpigmentation and hypopigmentation are common and sometimes scars and nail dystrophy may result. Genital adhesions resulting in dyspareunia, pain and bleeding are observed. Post-traumatic stress disorder is also possible in some patients.[26] Other complications may include: Gastroenterologic (esophageal strictures), Genitourinary (renal tubular necrosis, renal failure, penile scarring, vaginal stenosis), Pulmonary (tracheobronchial shedding with resultant respiratory failure), Cutaneous

(Scarring and cosmetic deformity, recurrences of infection through slow-healing ulcerations).[17]

Stevens-Johnson syndrome complications also include:

Secondary skin infection (cellulitis)

Cellulitis can lead to life-threatening complications, including sepsis.

Blood infection (sepsis)

Sepsis occurs when bacteria from an infection enter bloodstream and spread throughout the body. Sepsis is a rapidly progressing, life-threatening condition that can cause shock and organ failure.

Eye problems

The rash caused by Stevens-Johnson syndrome can lead to inflammation in eyes. In mild cases, this may cause irritation and dry eyes. In severe cases, it can lead to extensive tissue damage and scarring that results in visual impairment and, rarely blindness. Patient with Stevens Johnson syndrome, 27-50% progress to severe ocular disease. Ocular complications in this syndrome include: chronic cicatrizing conjunctivitis, corneal epithelial defects, corneal stromal ulcers, corneal perforation, endophthalmitis. Late ophthalmic complications are seen in up to 75% of patients.

Permanent skin damage

When the skin grows back following Stevens-Johnson syndrome, it may have abnormal bumps and coloring and have scars. Lasting skin problems may cause hair to fall out, and fingernails and toenails may not grow normally. Patient with Stevens Johnson syndrome, 27-50% progress to severe ocular disease. Ocular complications this syndrome include: chronic cicatrizing conjunctivitis, corneal epithelial defects, corneal stromal ulcers, corneal perforation, endophthalmitis. Other complications may include: Gastroenterologic (esophageal strictures), Genitourinary (renal tubular necrosis, renal failure, penile scarring, vaginal stenosis), Pulmonary (tracheobronchial shedding with resultant respiratory failure), Cutaneous (Scarring and cosmetic deformity, recurrences of infection through slow-healing ulcerations). [1,9,17]

PROGNOSIS

Prognosis is linked to rapid identification of the causative drug and its discontinuation. It is crucial to quickly establish proper clinical diagnosis, so that the causative drug may be discontinued and appropriate treatment is initiated. Patients with SJS caused by a drug have a better prognosis; the earlier the causative drug is withdrawn. [16] Sepsis is the main cause of death. SJS (with less than 10% of body surface area involved) has a mortality rate of around 5%. The risk for death can be estimated using the SCORTEN scale, which takes a number of prognostic indicators into account. It is helpful to calculate a SCORTEN within the first 3 days of hospitalization. In addition to the SCORTEN predictors, other factors determinant of poor prognosis includes late withdrawal of the causative drug and delay to transfer the patient to an aseptic or burn unit. Other outcomes include organ damage/failure, cornea scratching, and blindness. Restrictive lung disease may develop in patients with SJS after initial acute pulmonary involvement. Depending on the severity, the clinical course of SJS may last up to a few weeks. [24] SJS is an acute, self-limited disease, with high morbidity, that is potentially life threatening. Epidermal detachment may be extensive, to the entire skin surface. As in severe burns, fluid losses are massive, producing electrolyte imbalance. Super infection, thermoregulation impairment, excessive energy expenditure, alteration of immunologic functions and hematologic abnormalities are usual systemic complications. Age, percentage of denuded skin, neutropenia, serum urea nitrogen level, and visceral involvement are prognostic factors. After healing, altered pigmentation and corneal lesions are the main long-term complications. [28]

CONCLUSION

Successful management of SJS requires the early recognition of the conditions, diagnosis with biopsy, identification and removal of the causative drugs and intensive multidisciplinary management in a hospital with experienced medical and nursing personnel. [22] SJS is mainly caused by drugs, infections and probably other risk factors not yet identified. The pathogenesis of SJS 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 be capable of halting the

progression of skin detachment. [14] Supportive management is important to improve the patient's state. Despite all therapeutic efforts, mortality is high and increases with disease severity. Survivors may suffer from long-term sequelae such as strictures of mucous membranes including severe eye problems. Therefore, interdisciplinary care and follow-up of patients with SJS is very important. [10]

REFERENCES

1. Stevens-Johnson syndrome. MayoClinic.com. April 22, 2014; <http://www.mayoclinic.com/health/stevens-johnson-syndrome/DS00940/METHOD=print>.
2. Stevens-Johnson syndrome/toxic epidermal necrolysis. Genetics Home Reference (GHR). July 2015; <https://ghr.nlm.nih.gov/condition/stevens-johnson-syndrome-toxic-epidermal-necrolysis>.
3. Finkelstein Y, Macdonald EM, Li P, Hutson JR, Juurlink DN. Recurrence and mortality following severe cutaneous adverse reactions. *Jama*. 2014 Jun 4; 311(21):2231-2.
4. Paul MD, Sieving A. Facts about the Cornea and Corneal Disease. National Eye Institute, National Institutes of Health.
5. "Stevens-Johnson syndrome". GARD. Retrieved 26 August 2016.
6. Tan SK, Tay YK. Profile and pattern of Stevens-Johnson syndrome and toxic epidermal necrolysis in a general hospital in Singapore: treatment outcomes. *Acta Dermatovenereologica*. 2012 Jan 1; 92(1):62-6.
7. Lee HY, Tharmotharampillai T, Pang SM. Recurrence of Stevens-Johnson syndrome and toxic epidermal necrolysis in adults. *International journal of dermatology*. 2017 Apr 1; 56(4).
8. Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. *Journal of the American Academy of Dermatology*. 2008 Jan 31; 58(1):33-40.
9. Klein DM. Pathophysiology-Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis.
10. Chantaphakul H, Sanon T, Klaewsongkram J. Clinical characteristics and treatment outcome

- of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Experimental and therapeutic medicine*. 2015 Aug 1; 10(2):519-24.
11. Patel TK, Barvaliya MJ, Sharma D, Tripathi C. A systematic review of the drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Indian population. *Indian Journal of Dermatology, Venereology, and Leprology*. 2013 May 1;79(3):389.
 12. Stevens AM, Johnson FC. A new eruptive fever associated with stomatitis and ophthalmia: report of two cases in children. *American Journal of Diseases of Children*. 1922 Dec 1;24(6):526-33.
 13. Maverakis E, Wang EA, Shinkai K, Mahasirimongkol S, Margolis DJ, Avigan M, Chung WH, Goldman J, La Grenade L, Pirmohamed M, Shear NH. Stevens-Johnson Syndrome and toxic epidermal necrolysis standard reporting and evaluation guidelines: results of a National Institutes of Health working group. *JAMA dermatology*. 2017 Jun 1.
 14. Khalili B, Bahna SL. Pathogenesis and recent therapeutic trends in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Annals of Allergy, Asthma & Immunology*. 2006 Sep 1;97(3):272-81.
 15. Morel E, Escamochero S, Cabañas R, Díaz R, Fiandor A, Bellón T. CD94/NKG2C is a killer effector molecule in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *Journal of Allergy and Clinical Immunology*. 2010 Mar 31;125(3):703-10.
 16. Schmidt D, Kluge W. Fatal toxic epidermal necrolysis following reexposure to phenytoin: a case report. *Epilepsia*. 1983 Aug 1;24(4):440-3.
 17. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology*. 2005 Apr 12;64(7):1134-8.
 18. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Archives of Dermatology*. 2000 Mar 1;136(3):323-7.
 19. Kardaun SH, Jonkman MF. Dexamethasone pulse therapy for Stevens-Johnson syndrome /toxic epidermal necrolysis. *Acta dermato - venereologica*. 2007 Mar 15;87(2):144-8.
 20. Hashim N, Bandara D, Tan E, Ilchshyn A. Early cyclosporine treatment of incipient toxic epidermal necrolysis induced by concomitant use of lamotrigine and sodium valproate. *ACTA DERMATOVENEREOLOGICA-STOCKHOLM-*. 2004 Jan 1;84(1):90-.
 21. Valeyrie-Allanore L, Wolkenstein P, Brochard L, Ortonne N, Maitre B, Revuz J, Bagot M, Roujeau JC. Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. *British Journal of Dermatology*. 2010 Oct 1;163(4):847-53.
 22. Mockenhaupt M. Stevens-Johnson syndrome and toxic epidermal necrolysis: clinical patterns, diagnostic considerations, etiology, and therapeutic management. In *Seminars in cutaneous medicine and surgery* 2014 Mar 1 (Vol. 33, No. 1, pp. 10-16). *Frontline Medical Communications*.
 23. Thong BY. Stevens-Johnson syndrome/toxic epidermal necrolysis: an Asia-Pacific perspective. *Asia Pacific Allergy*. 2013 Oct;3(4):215.
 24. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet journal of rare diseases*. 2010 Dec 16; 5(1):39.
 25. Mockenhaupt M. The current understanding of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Expert review of clinical immunology*. 2011 Nov 1.
 26. Bentley, John; Sie, David (8 October 2014). "Stevens-Johnson syndrome and toxic epidermal necrolysis". *The Pharmaceutical Journal*. 293 (7832). Retrieved 8 October 2014.
 27. Schöpf E, Stühmer A, Rzany B, Victor N, Zentgraf R, Kapp JF. Toxic epidermal necrolysis and Stevens-Johnson syndrome: an epidemiologic study from West Germany. *Archives of dermatology*. 1991 Jun 1; 127(6):839-42.
 28. French LE. Toxic epidermal necrolysis and Stevens Johnson syndrome: our current understanding. *Allergology International*. 2006; 55(1):9-16.