

Anatomy, physiology and drugs triangular dynamics in Steven Johnsons syndrome

Abstract

The incidence of Steven-Johnson syndrome has been on the increase within the last two years in Nigeria. This renewed the interest on this disease to explore the dynamics for improved patient care. This review outlined the relationship between anatomic or structural changes, physiological variations, and the effect of drugs in Steven Johnson's syndrome. Better understanding of the fundamental structural and physiological changes in affected patients is vital to improve the treatment and/or the initial management procedures in resource-limited environments. This article showed the relationship between structural features, functions, and treatment. Tailoring treatment to the anatomical, physiological changes, and the effect of drugs and causative agents suggests a triangular dynamic trend in the disease state management.

Keywords: epidermal cells, necrolysis, drugs, membranes, steven johnsons syndrome

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Introduction

Stevens-Johnson syndrome, (SJS) is a life-threatening skin disorder characterized by toxic epidermal necrolysis, in which cell death causes the epidermis to detach from the dermis. The syndrome is a hypersensitivity complex that affects the skin and the mucous membranes. The syndrome is caused by certain medications (such as lamotrigine), but it can also be due to infections, or more rarely, cancers, or hypersensitivity reaction to some compounds.^{1,2} The blisters and erosions in SJS cover between 3% and 10% of the entire body surface.³ It is associated with factors ranging from immunoreactions, infections, genetic factors, and adverse drug reactions.^{4,5} Immunocompromised patients who are slow acetylators and brain tumor patients on anticonvulsant drugs who are undergoing radiotherapy are usually more prone to SJS.⁶

The incidence is estimated at 1.1 and 7.1 cases per million per year and higher in Africa due to high use of crude drugs and HIV prevalence.⁷ Better understanding of the fundamental structural and physiological changes in affected patients is essential towards improving the treatment and/or the initial management procedures in resource-limited environments. This article simplified and brought to the fore the relationship between anatomic structure, physiology, and causes of SJS, which could be utilized in resource, limited settings in patients management. It showed the relationship between structural features, functions, and treatment.^{2,4,8,9} This review outlined the relationship between anatomic or structural changes, physiological variations, and the effect of drugs in Steven Johnson's syndrome.

Discussion

The manifestation of SJS is usually multifaceted affecting varying degree of body surfaces and structures. Treatments are usually merely supportive, symptomatic, and dependent on the percentage of body surface, the structures affected, and the degree of damage done to the affected structures.¹⁰ Following generalized cellular deterioration accompanying the disease process, damaging cellular effects can take place at the tissue levels precipitating depression of mitochondrial activities, reduction of sodium and potassium transport across cell membranes leading to accumulation of sodium and chlorides in the

cells and loss of potassium and subsequent swelling of cells. Lysosomal activities ensue leading to intracellular deterioration.¹¹ Cells adjacent to venous end of capillaries with can suffer nutritive deficiency. This can lead to tissue necrosis in severe shock. Cardiac output and arterial pressure often decrease in anaphylactic conditions leading to the release of histamine and histamine like substances with a net effect of reduction in mean venous return and its catastrophic consequences.¹² Epithelial tissues cover body surfaces, line the cavities, and serve as interface tissue for protection, absorption, excretion, filtration, sensory perception, and secretion. These anatomical and physiological functions are altered to varying degrees in SJS.

Disruption of this structure and function lead to loss of body fluids containing proteins and electrolyte. Dehydration and electrolyte imbalance ensues leading to further alteration of homeostasis. This forms one of the bases of therapy. Microorganisms multiply rapidly in the nutrient-rich structures dead and protein rich body fluid bathed-tissues. Infection threats associated with loss of skin barrier. This forms the basis for antibiotic use in therapy.¹³ Other signs and symptoms in SJS are associated with structural and physiological defects, which disrupt normal physiological mechanisms as shown in Table 1. Additional physiological and pathophysiological manifestations include fatigue, fever, and sore throat. The pathophysiological manifestations form the basis of management, employed in patient management in resource-limited settings. The management procedures will depend on the degree of manifestation, percentage of body surface affected, causes and other presenting signs and symptoms.^{5,14} Other treatment modalities based on prompt recognition of causative agents and organisms as shown in Table 2. Retrospective studies suggested that use of corticosteroids is controversial because of associated increase in hospital stay and resultant increase in complication rates. The use of cyclophosphamides and cyclosporins did not offer better therapeutic outcomes. Use of antiseptics and topical anesthetics is very common and essential in resource-limited settings. Ophthalmological team should be invited or consulted in corneal vascularization and other ophthalmic complications.¹⁵⁻¹⁸

Erythema multiforme major (EMM) is different from SJS despite their similarities. This was clearly delineated in 1993.^{19,20} Studies have shown that antibiotics, anticonvulsants, and NSAIDs trigger

SJS very often.^{19,21} However, drug induced SJS has been poorly reported.²² Report by Stevens Johnson Syndrome foundation (SJSF), has shown that commonly used over-the-counter medications like paracetamol, amoxicillin, and ibuprofen, and herbal products with Ginseng can trigger SJS and TEN.^{23,24} SJS has been tailored to viral and Mycoplasma pneumonia without previous sensitization.^{19,25-30} Studies in immunocompromized patients show that they are more susceptible to SJS.^{18,30-35} This suggests genetic inclination to the

varying manifestations of SJS.³⁶ Immunoglobulin preparations administered intravenously showed good outcomes in reduction of the duration of skin reactions and reduction of pathophysiological manifestations like symptoms.³⁷⁻³⁹ Discontinuation of triggering substances and use of high dose corticosteroids has shown promising outcomes in therapy.⁴⁰ Adjuvant therapy like plasmapheresis has been beneficial in SJS cases.⁴¹⁻⁴⁶

Table 1 Relationship between Anatomical basis and Physiological/pathophysiological manifestations of SJS

Timing	Anatomical basis	Physiological/pathophysiological manifestations
Early stage	Basket weave-like stratum corneum	Full-thickness epidermal necrosis
	Dermis and epidermis	Fever, sore throat, running nose, fatigue, general aches and pains, ulcers in mouth, genitals, anal regions as well as conjunctivitis
	Confluent epidermal necrosis	Minimal associated inflammation
	Death of keratinocytes, less than 10% external epidermal detachment	Separation of the epidermis from the dermis
	DNA disorganization	Recruitment of more chemokines from dieing cells
Advanced stage	Erythematous, flat and purpuric lesions	Pigmentation problems, skin scarring, scarred genitals, joint pains, lung diseases, obstructive disorders and eye complications, adhesions, ulcers, and blindness.
	Epidermal necrolysis	Inflammation of epidermal cells and death of affected cells
	Dehydration	Thromboembolism and disseminated intravascular coagulation
	Gastrointestinal ulceration, necrolysis, strictures and perforation	Acute malnutrition
		Shock and multi-organ failure

Table 2 Relationship between the likely causes of SJS, pathophysiological changes, and likely interventions

Implicated organisms	Implicated infections	Implicated drugs/agents	Pathophysiological changes	Likely interventions
Viruses	-Herpes (<i>herpes simplex</i> or <i>herpes zoster</i>); -Pneumonia -HIV -Hepatitis -Mumps -Influenza <i>Coxsackie virus</i> - <i>Epstein-Barr virus</i> - <i>Enteroviruses</i>	<ul style="list-style-type: none"> Analgesics Allopurinol, Acetaminophen Antibiotics Penicillin, Antipsychotics Radiation therapy Sulfonamides: Trimethoprim-sulfamethoxazole Sulfadiazine Sulfasalazine 	-Corneal vascularization -Mouth ulcer -Mucosal involvement: erythema, oedema, sloughing, blistering, ulceration and necrolysis. -Eye: conjunctivitis, corneal ulcerations. -Genital: erosive vulvovaginitis or balanitis	-Cessation of suspected drugs -Hospital Admission: Preferably in burns unit/ intensive care -Nutritional and fluid replacement -Temperature maintenance
	Bacteria	-Group A beta-hemolytic streptococci, diphtheria, <i>Mycoplasma pneumoniae</i> , lymphogranuloma venereum, <i>mycobacteria</i> , rickettsial infections, tularemia, brucellosis, and typhoid	<ul style="list-style-type: none"> Antiviral agents: Nevirapine Abacavir Anticonvulsant: Phenobarbital Phenytoin Valproic acid Carbamazepine Lamotrigine Imidazole antifungal agents Non-steroidal anti-inflammatory drugs (oxicam type such as meloxicam). Salicylates Sertraline Bupropion 	-General examination: fever, tachycardia, hypotension; altered level of consciousness, seizures, coma. -Skin: Lesions may occur anywhere, non pruritic urticarial lesions -Lung: mucosal shedding -Vaginal stenosis and penile scarring -Renal tubular necrolysis and acute kidney injury may occur -Gastrointestinal ulceration
Fungus	-Dermatophytosis, and histoplasmosis have been considered as possible causes of SJS			-Mouth-care _Cyclophosphamide and cyclosporin -Intravenous immunoglobulin -Topical pain anaesthetics and antiseptics, -Nasogastric or parenteral feeding -Oral macrolide or oral doxycycline
Protozoa	<u>Malaria and trichomoniasis</u>			

Conclusion

Disruption of physiological functions in SJS is associated with resultant alteration in structural/anatomical functions leading to myriads of clinical manifestations associated with the disease state. These manifestations form the basis for management of SJS, utilized in resource-limited settings where specialist care and equipment are non-accessible. Simple understanding of the anatomical and pathophysiological basis, and subsequent selection of treatment options based on the underlying cause and degree of progression could be a vital means of averting its progression to critical states and subsequent loss of lives especially in developing countries. Tailoring treatment to the anatomical, physiological changes, and the effect of drugs and causative agents suggests a triangular dynamic trend in the disease state management. Disease process is a dynamic one. Saving lives should be paramount before accessing specialist care especially in places where immediate specialist care could not be imminent. Elimination of all suspected agents and drugs, fluid replacement where possible and microbial protection with antibiotics based on clinicians discretion is vital to arresting further disease progression, restoring normal physiological functions and ultimately saving lives in remote and resource limited settings before referral for specialist care.

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Conflict of interest

Author declares that there is no conflict of interest.

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