STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS: PANORAMIC REVIEW

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SUMMARY

Introduction: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are infrequent diseases represented by disseminated epidermal necrosis and skin sloughing. They have a representative mortality and morbidity, their early diagnosis and treatment is necessary to provide good results in affected individuals.

Objective: to detail the current information related to Stevens-Johnson syndrome and toxic epidermal necrolysis, description, clinical presentation, pathophysiology, diagnosis, differential and treatment.

Methodology: a total of 52 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 44 bibliographies were used because the other articles were not relevant for this study. The sources of information were PubMed, Google Scholar,CrossRef, and Cochrane; the terms used to search for information in Spanish, Portuguese, and English were: Stevens-Johnson, toxic epidermal necrolysis, and immunologic burn.

Results: Almost all affected individuals present mucosal involvement, with two or more mucosal surfaces involved in up to approximately 80% of the cases. Oral involvement is more frequent, accompanied by mucositis and ulceration in almost all cases. Ocular involvement is also frequent in 60-100% of patients with SJS/TEN, and can present as conjunctival hyperemia and sometimes even complete epidermal detachment of the ocular surface. Gynecologic involvement also varies according to severity, however it is seen in approximately 77% of affected individuals. The precise incidence of genitourinary involvement in individuals affected in the acute phase of SJS/NET is not known. Drugs are the factors most frequently associated with SJS and NET, however, infection, especially Mycoplasma pneumonia, has been implicated. In approximately 15-30% of cases, no causative agent can be identified.

Conclusions: SJS-NET are devastating and potentially fatal mucocutaneous diseases. Prior to skin alteration, there is a prodromal phase of symptoms, such as general malaise, fever, pharyngeal pain and cough. Later the skin and mucous membranes are affected, traditionally appearing as erythematous

macules or atypical target lesions on the trunk that progress to confluent areas of erythema with dark centers, sheets of denuded epidermis and flaccid blisters presenting positive Nikolsky's sign. According to the improvement in early care and the improvement of supportive care the mortality in SJS and NET will continue to decrease. The most important act in the acute phase is immediate withdrawal of the culprit drug when there are signs of SJS-NET, the signs are blisters or erosions that distinguish these can reduce mortality. General supportive care is the mainstay of treatment.

KEY WORDS: *toxic epidermal necrolysis, Stevens-Johnson, skin, immunologic.*

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare diseases represented by disseminated epidermal necrosis and skin sloughing. They have a representative mortality and morbidity, their early diagnosis and treatment is necessary to provide good results in affected individuals. At the moment it is thought that these 2 entities present similar pathophysiology and are divided according to the body surface area (BSA) involved(1,2).

The clinical presentation of these diseases outside of the skin, eyes and oral mucosa is not clearly determined, therefore, sometimes they are not clinically raised. According to the development of supportive care, mortality from SJS and NET is decreasing; moreover, chronic complications in the altered organ systems are becoming more and more common, so the investigation of early symptoms and signs of SJS-NET is essential for proper care. These skin disorders, also called immunological burns, can be fatal, with a mortality rate of approximately 35%. The responsible drugs are identified in approximately 85% of SJS-TEN cases(3).

METHODOLOGY

A total of 52 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 44 bibliographies were used because the information collected was not important enough to be included in this study. The sources of information were Cochrane, PubMed, CrossRef and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: Stevens-Johnson, toxic epidermal necrolysis, immunologic burn.

The choice of bibliography exposes elements related to Stevens-Johnson syndrome and toxic epidermal necrolysis, description, clinical presentation, pathophysiology, diagnosis, differential and treatment.

DEVELOPMENT

Description.

SJS/NET is described as a generalized vesiculopustular rash plus epidermal detachment and necrosis, with involvement of mucous membranes, mostly that of the eyes, mouth and skin. The degree of total body surface area (TBSA) affected shows where on the SJS/NET spectrum an individual is affected.

SJS: <10 % TBSA.

SJS-TEN overlap: 10-30 % TBSA.

TEN: >30% TBSA.

Both entities, SJS and NET, are now often referred to together as a single entity Epidermal Necrolysis (EN). SJS and NET usually occur as an idiosyncratic reaction to systemic drugs, among which antibiotics, nonsteroidal anti-inflammatory drugs and antiepileptic drugs are frequently associated. In 15% of the cases, it is not possible to distinguish the drug cause that initiated the disease. These 2 entities are often also due to viral infections, vaccines and other non-drug provocateurs. The ALDEN algorithm or algorithm of drug causality for EN, simplifies to know the responsible drug in cases of SJS and NET, this ALDEN algorithm gives a final score according to six criteria to find if it is "very probable", "probable", "possible", "unlikely" and "very unlikely" that a drug has generated a SJS-TEN. These criteria also allow to rule out drugs that are unlikely to be placed as the origin of SJS-NET(3,4).

Table 1. ALDEN algorithm criteria and scoring for drug causality.

Criteria	Possible score
Time lag between initial drug intake to onset of reaction (index day)	−3 to +3
Presence of drug in the body on index day	0 to −3
Prechallenge/rechallenge outcome with the suspect drug	−2 to +4
Outcome of rechallenge	0 to −2
Drug notoriety for causing SJS/TEN	−1 to +3
Other possible etiologic alternatives	−1, if applicable

The total ALDEN is based on the six criteria listed. A total score of ⩾6 is categorized as very probable, 4–5 as probable, 2–3 as possible, 0–1 as unlikely, and <0 as very unlikely. Specifics of the scoring system for each criterion is not described here but can be found in Sassolas and colleagues.

ALDEN, algorithm of drug causality for epidermal necrolysis; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Source: Shanbhag SS, Chodosh J, Fathy C, Goverman J, Mitchell C, Saeed HN. Multidisciplinary care in Stevens-Johnson syndrome(3).

Clinical Presentatio.

Prior to skin alteration there is a prodromal phase of symptoms, such as general malaise, fever, pharyngeal pain and cough. Later the skin and mucous membranes are affected, traditionally appearing as erythematous macules or atypical target lesions on the trunk that progress to confluent areas of erythema with dark centers, sheets of denuded epidermis and flaccid blisters presenting positive Nikolsky's sign. Almost all affected individuals present mucosal involvement, with two or more mucosal surfaces involved in up to approximately 80% of the cases. Oral involvement is more frequent, accompanied by mucositis and ulceration in almost all cases. Ocular alteration is also frequent in 60-100% of patients with SJS/TEN, and may present as conjunctival hyperemia and sometimes even develop a complete epidermal detachment of the ocular surface. Early

consultation with an ophthalmologic specialist is essential to prevent long-term ocular sequelae, which occur in 20-79% of SJS/TEN survivors and include keratinization of the eyelid margins, dry eye, ocular surface xerosis, loss of corneal epithelial stem cell function and opacification. Gynecologic involvement also varies according to severity, but is seen in approximately 77% of affected individuals. The precise incidence of genitourinary involvement in individuals affected in the acute phase of SJS/TEN is not known; however, some studies report that approximately 71% of children with SJS/TEN had genitourinary involvement in the acute phase, with penile erosions being the most common, as well as meatal involvement, which in the acute phase generated dysuria and hematuria. Other complications such as otorhinolaryngological, digestive, pulmonary, psychiatric and nutritional can also occur (1,3,5-10).

Figure 1. Toxic epidermal necrolysis due to carbamazepine

Source: Frantz R, Huang S, Are A, Motaparthi K. Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis(1).

Pathophysiology

Drugs are the factors most frequently related to SJS and NET, however, infection, especially Mycoplasma pneumonia, has been implicated. In approximately 15-30% of cases, no causative agent can be identified. The specific pathophysiology is still not 100% clear, however the triggering factors of the diseases have been well observed. They are thought to be T-cell mediated type IV hypersensitivity reactions.

There are currently some hypotheses as to how drugs produce an immune response to give rise to SJS-NET:

➢ Haptene/pro-haptene: small molecule drugs will covalently bind to serum proteins, creating a complex recognized by some HLA molecules and presented to T cells to produce an immune response.

➢ Pharmacological interaction (pi): chemically inert drugs, which cannot covalently bind to serum proteins, bind directly to HLA molecules, resulting in T-cell activation.

➢ Altered peptide: the drugs bind inside the HLA binding pockets in a way that changes the presentation of self proteins to T cells so that they are no longer recognized as self, generating an immune response.

The end result is activation of T cells in reaction to a drug or infection and downstream epidermal necrosis.

Early hypotheses presented that keratinocyte death was through interactions of soluble Fas ligand (sFasL) with the Fas receptor on the surface of keratinocytes; later it was shown that granulysin was the most notable mediator of apoptosis and the levels of these in the fluid of the blisters correlated with the severity of the disease, granulysin is the major driver of epidermal necrosis, however it does not work alone. Studies show increased serum levels of 28 different cytokines and chemokines in patients with SJS-TEN, among which granulysin and IL-15 were directly related to disease significance. In other studies evaluating the role of programmed necrosis, they found that they contribute to

keratinocyte degeneration, generating remarkable diagnostic implications. The understanding of the pathogenesis is still not well elucidated. Drug-induced SJS-NET may be generated by dysregulation of cell-mediated immunity, cytotoxic T lymphocytes (CTL) and natural killer (NK) cells(1,7,11-14).

Differential Diagnosis.
Prior to the diagnosis of SJS/NET, a broad differential diagnosis should be made in order to avoid misdiagnosis. It is important to differentiate from other vesiculopustular and desquamative dermatoses, such as linear IgA bullous dermatosis, pemphigus vulgaris, erythema multiforme major (EMM) and staphylococcal scalded skin syndrome (SSSS). It is of importance to recognize that, previously erythema multiforme major and SJS-NET were divided as components of the same range of diseases, due to the almost identical clinical and histopathological presentation, they were later shown to be different diseases. Therefore, the diagnosis has to be made under clinical standards(1,5,6,15-18).

Diagnosis.
Potential Biomarkers.
Rapid diagnosis of SJS/TEN is paramount to suppress the offending agent, initiate complementary and supportive therapies and improve the final outcome. However, the clinical manifestations can be almost identical to that of the different blistering disorders and diagnosis can sometimes be difficult. The diagnosis of these disorders are time sensitive, frozen sections can be used to select early. SJS-NET can be differentiated from SSSS by the amount of epidermal detachment, being subcorneal in SSSS and occurring at the dermoepidermal junction in SJS-NET. In the histopathology of SJS-NET there is generalized keratinocytic necrosis which is representative of the entity. Differentiating between SJS-NET and MME is complicated due to the similar histopathology. In both entities in early stages a vacuolar or lichenoid interface with scattered necrotic keratinocytes is observed. Depending on the course of the disease, subepidermal excision with increased epidermal necrosis is differentiated. A thicker lymphocytic infiltrate suggests MME, while the increase of eosinophils and confluent epidermal necrosis suggest SJS-NET, however, these distinctions are not reliable and require a clinicopathological link(1,19,20).

Multiple clinical trials have shown results of possible diagnostic markers of the disease, such as elevated granulysin level even before skin detachment and mucosal involvement, granulysin correlates in these studies with disease significance in SJS-NET. Despite this, the same findings found in these pathologies were also present in other cytotoxic T-lymphocyte (CTL)-mediated blistering blistering disorders, such as blistering drug-fixed eruption (BFDE) and MME. High serum granulysin levels were also observed in drug-reactive individuals with eosinophilia and systemic symptoms (DRESS). Concluding that although granulysin is increased in serum and blister fluid, it is not a

specific finding for SJS-NET, and is therefore of limited use for timely diagnosis at the moment(1,12,21,22).

The nonspecific cytokine CCL-27 probably plays an important role in the pathogenesis of SJS-NET, collaborating in the passage of T cells into the skin at sites of inflammation. Studies show its elevation in the skin and serum especially in the acute phase of SJS-NET, however, this implies that CC also identified elevated levels of CCL27 in exanthem produced by non-blistering drugs, so its use is also limited(1,23,24).

Serum galectin-7 also correlated with disease severity in patients with SJS-NET and significantly higher levels in the acute phase and decreased levels in the late phase of the disease. Galectin-7 could therefore be a potential mediator of SJS-NET and a useful biomarker for diagnosis(1,25).

Necroptosis differs from apoptosis in that cell death is the consequence of external triggers that modify membrane permeability and generate cell lysis without the collaboration of caspases. Several current studies have demonstrated RIP3 receptor-interacting kinase-3 as an important mediator, confirming that necroptotic keratinocytes release RIP3 in the serum of affected individuals, its levels being directly related to the level of necroptosis and the significance of the disease. RIP3 levels in the serum of individuals with MME with SJS-NET are markedly higher than individuals with MME, so this biomarker can be used to distinguish between these pathologies(1,26,27).

Studies demonstrated a similar reaction to SJS-NET in Mycoplasma pneumoniae infection, the so-called Mycoplasma pneumoniae-induced mucositis (MIRM). Some patients had significant mucosal involvement with minor skin involvement and better prognosis when compared to SJS-NET. This was classified apart from SJS-NET and MME. Many other studies implicate different infections as generators of MIRM-like reactions, such as adenovirus, influenza B and Chlamydia pneumoniae(1,28).

Subsequently, a new classification for blistering disorders in pediatric patients was proposed. Where SJS, SJS/TEN and TEN are lumped together into a single disorder named drug-induced epidermal necrolysis (DEN). Cases of infection, severe mucosal involvement and relatively minor cutaneous involvement were considered separately and called reactive infectious mucocutaneous eruption (RIME). Erythema multiforme (EM) was placed as a distinct disease from DEN and RIME . This classification is useful because of the different treatment of DEN and RIME; in RIME, identification and treatment of the underlying infection is needed, followed by supportive care and possible antimicrobial and immunosuppressive therapies, in DEN, identification and removal of the causative drug is needed followed by supportive care and probable immunosuppressive therapy. More clinical studies are needed to better establish management strategies for DEN and RIME(1,29,30).

Figure 2. SJS/TEN, síndrome de Stevens-Johnson/necrólisis epidérmica tóxica.
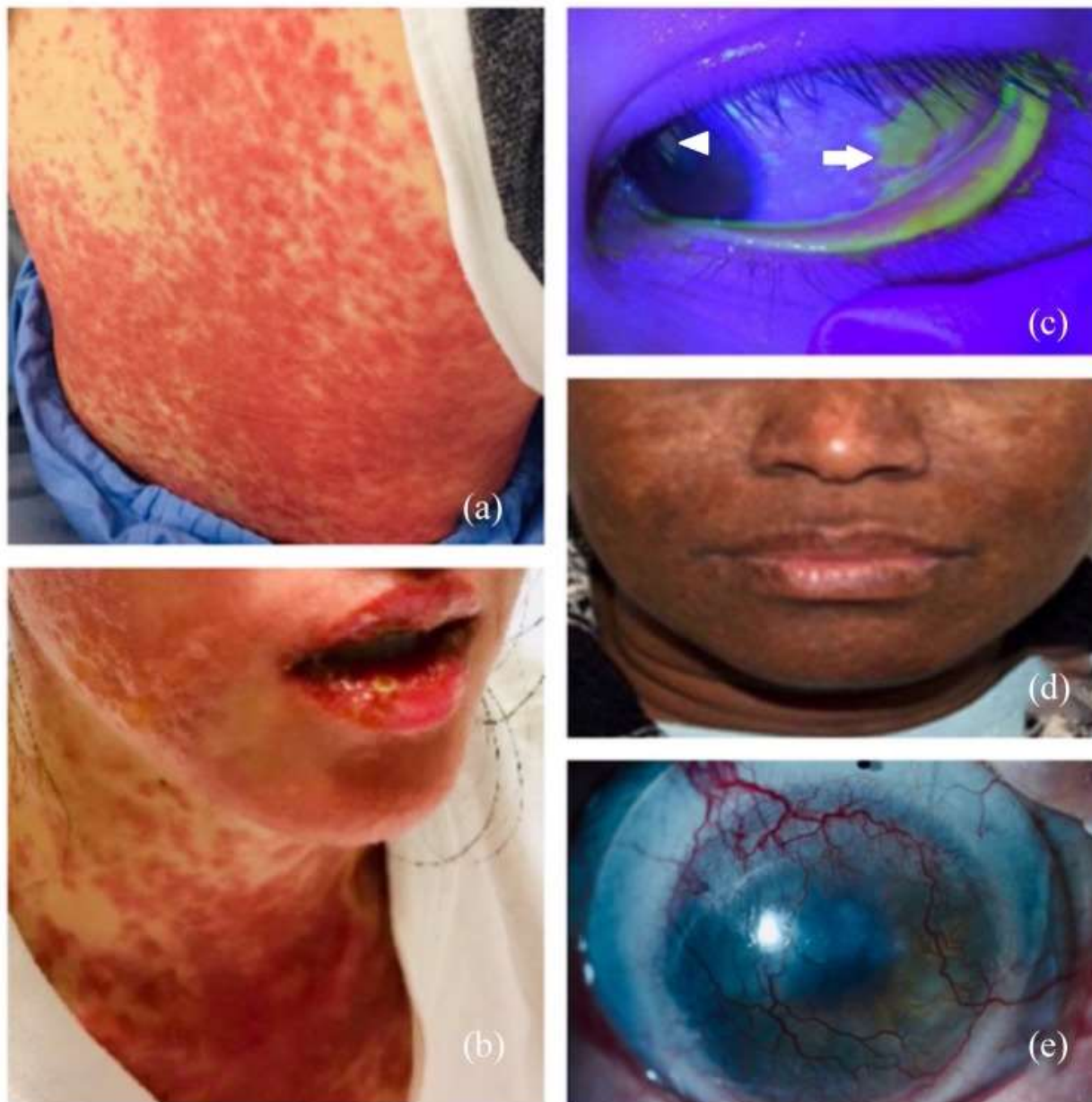
Source: Shanbhag SS, Chodosh J, Fathy C, Goverman J, Mitchell C, Saeed HN. Multidisciplinary care in Stevens-Johnson syndrome(3).

Non-Pharmacological Treatment.

Supportive care is the cornerstone of treatment in individuals affected with SJS/NET, this includes immediate withdrawal of the offending drug being the most important, in addition to infection control, fluids, electrolytes and wound care. Prompt withdrawal of the suspect drug at the onset of blistering or erosions reduces mortality(1,3,31).

Adequate fluid, electrolyte and nutritional management is of vital importance as it reflects the needs of burn patients due to insensible losses. Fluid needs are about 30% less in individuals with SJS-NET compared to individuals with burns. A warm environment between 30 to 32 °C should be maintained because of the loss of thermoregulatory function of the skin. Fluids should be monitored to maintain a diuresis of 0.5 to 1 ml/kg/h. Enteral feeding should be started early and nasogastric tube feeding should be used if necessary(1,32,33).

Prophylactic antibiotics do not improve outcomes, however, proper wound care and sterile management are imperative to reduce the rate of infection. Surgical debridement is controversial. Anti-shear therapy is an option to surgical debridement and decreases hospital costs and pain, so more studies and better evidence are needed to fully understand the role of this therapy(1,34-36).

Pharmacological Treatment

At the moment there is no standard of care when it comes to pharmacological treatment. It is thought that immunosuppressive therapies will improve treatment, and there are already cases with beneficial results with various combined treatment options such as corticosteroids, IVIG, cyclosporine and TNF-alpha inhibitors(1,11,37,38).

It is complex to differentiate whether disease remission was due to treatment or was the natural course of the disease. The role of corticosteroids as sole therapy is still debated, as well as the performance of IVIg(1,24,39).

Cyclosporine has shown positive results in several studies to this point. In several studies and meta-analyses it was shown that the only therapy that showed statistically significant improvements in outcomes was the combination of IVIG and corticosteroids and it is also reported that cyclosporine shows promising results (with or without IVIG), IVIG and plasmapheresis and etanercept, however more studies are needed(1,40-42).

Another study showed that patients who received plasmapheresis had a lower disease severity score over the course of the disease(1,43).

TNF-alpha inhibitors are also of interest due to their immunosuppressive effects. Due to the absence of consensus on the most effective drug therapy in SJS and NET, issues such as monetary value may be kept in mind when discussing the course of treatment(1,44).

CONCLUSIONS

SJS-NET are devastating and potentially fatal mucocutaneous diseases. Prior to skin involvement, there is a prodromal phase of symptoms, such as malaise, fever, pharyngeal pain and cough. Later the skin and mucous membranes are affected, traditionally appearing as erythematous macules or atypical target lesions on the trunk that progress to confluent areas of erythema with dark centers, sheets of denuded epidermis and flaccid blisters presenting positive Nikolsky's sign. According to the improvement in early care and the improvement of supportive care the mortality in SJS and NET will continue to decrease. The most important act in the acute phase is the immediate withdrawal of the culprit drug when there are signs of SJS-NET, the signs are blisters or erosions that distinguish these can reduce mortality. Drugs are the factors most frequently related to SJS and NET, however, infection, especially Mycoplasma pneumonia, has been implicated. In approximately 15-30% of cases, no causative agent can be identified. General supportive care is the mainstay of treatment.

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Conflict of Interest Statement

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