Chapter 25

STEVENS-JOHNSON SYNDROME

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Stevens-Johnson Syndrome (SJS) is a severe, potentially fatal delayed hypersensitivity reaction affecting the skin. This condition can be triggered by various drugs, especially anticonvulsants, antibiotics, and anti-inflammatory drugs. Besides pharmacological causes, infections by certain microorganisms like viruses and bacteria, or the presence of some neoplasms, can also trigger the disease. SJS has a high mortality rate

in Brazil, ranging from 20% to 25%. The annual incidence is 1.2 to 6 cases per million inhabitants, being more prevalent in adult men (Vieira *et al.*, 2021).

In the prodromal period of SJS, nonspecific symptoms include fever, conjunctival itching, paresthesia, sensitivity to touch, and a burning sensation on the skin. This is followed by the abrupt onset of skin erythema, which can evolve from macules to papules, blisters, confluent erythema, vesicles, or urticaria plaques, usually without itching. Lesions are most common on the face, neck, chest, and mucous membranes. Treatment of SJS requires the immediate identification and suspension of the triggering agent. Early recognition of clinical signs and detection of the etiological agent are crucial for a positive prognosis. Efficient diagnosis, based on clinical signs and biopsy when necessary, is essential for patient recovery (Campos; Cintra and Ximenes, 2023).

Systemic treatment options are still limited and not always effective (Dourado; Ribeiro, 2023). SJS represents a public health challenge due to the difficulty of early diagnosis, indiscriminate use of medications by the population, complex management of severe complications, and the scarcity of specific screening tests (Leite *et al.*, 2024). Recently, diagnostic trends have focused on the use of predictive biomarkers to identify patients predisposed to adverse drug reactions. Additionally, research on the disease's pathophysiology is increasing to identify more specific therapeutic targets (Ribeiro; Ribeiro and Benito, 2017).

Proper treatment is vital for managing patients, relieving symptoms, and preventing infections. This includes topical treatment, such as creams and ointments, and systemic treatment involving corticosteroids, analgesics, immunoglobulins, cyclosporins, and antibiotics in case of sepsis (Campos; Cintra and Ximenes, 2023). Treatment should be personalized and often performed in Intensive Care Units (Dourado; Ribeiro, 2023). The complexity of Stevens-Johnson Syndrome represents a significant public health threat, highlighting the relevance of studies to improve clinical approaches and outcomes for affected patients (Campos; Cintra and Ximenes, 2023).

EPIDEMIOLOGY

The incidence of SJS increases with age, being more prevalent in adult men aged 20 to 53 years, although it can affect all age groups (Vieira *et al.*, 2021). Women, however, are more prone to experiencing adverse reactions due to differences in body weight, hormonal variations, more frequent medical consultations, and greater adherence to medical prescriptions (Dewi, 2019).

Various predisposing factors influence the incidence of these conditions, such as concomitant medical conditions, use of multiple medications, genetic predisposition, and immunosuppression. For instance, patients with HIV have an increased incidence up to 1000 times compared to the general population, with a rate of 1 case per 1,000 patients per year. Other factors include the presence of cancer and concurrent use of radiotherapy and anticonvulsants (Dewi, 2019).

Geographically, 90% of SJS cases involve hemorrhagic and painful mucosal involvement, especially in the oral, ocular, and genital mucosa. The location and extent of lesions vary among individuals, being more frequent in conjunctival, urethral, and oropharyngeal areas (Vieira *et al.*, 2021). Lesions include macules, papules, blisters, urticaria plaques, confluent erythema, and papules, which may have a purpuric, necrotic, or vesicular center, coalescing and displaying a positive Nikolsky sign (Ribeiro; Ribeiro and Benito, 2017).

SJS is mainly related to drug use due to delayed hypersensitivity reactions to certain substances in medications. Risk factors that increase this prevalence include infections, immunosuppressive disorders, and certain specific types of human leukocyte antigens. Additionally, multiple comorbidities, medication use, and diseases that activate the immune system are predisposing factors for developing SJS (Vieira *et al.*, 2021).

DIAGNOSIS

Early diagnosis of SJS and Toxic Epidermal Necrolysis (TEN) is challenging since, in their early stages, these dermatological conditions resemble other skin diseases. Due to the high mortality rate, a rapid diagnosis is crucial to improve the patient's prognosis (Caminha *et al.*, 2021).

SJS/TEN generally begins one to three weeks after contact with the etiological agent. In the initial stage, symptoms are nonspecific, including general malaise, fever (39-40°C), anorexia, rhinorrhea, asthenia, odynophagia, headache, myalgia, arthralgia, conjunctival itching, paresthesia, sensitivity to touch, and a burning sensation on the skin. These symptoms vary in intensity and duration, persisting for approximately one week.

The most characteristic sign of SJS/TEN is skin erythema, which appears abruptly as irregular, confluent erythematopurpuric macules with a "target" appearance. As the disease progresses, papular lesions and flaccid grayish blisters develop (Martínez-Cabriales; Gómez-Flores and Ocampo-Candiani, 2015). The Nikolsky sign, where superficial friction of the skin causes epidermal detachment, may be present and indicates the separation of the epidermis (Dourado; Ribeiro, 2023).

Lesions start on the trunk and later affect the neck, face, and upper limbs bilaterally and symmetrically (Martínez-Cabriales; Gómez-Flores and Ocampo-Candiani, 2015). They can occur anywhere but are most common on the face, neck, and chest (Dourado; Ribeiro, 2023). The extent of lesions is assessed based on the total number of blisters and areas positive for the Nikolsky sign. They are classified as follows (Sacoto, 2023):

- Stevens-Johnson Syndrome: Lesion on less than 10% of the body surface.
- Overlap between SJS and TEN: Lesion on 10-30% of the body surface.
- Toxic Epidermal Necrolysis: Lesion on more than 30% of the body surface.

Mucosal involvement occurs in 90% of patients and can be an indicator of progression from SJS to TEN (Martínez-Cabriales; Gómez-Flores and Ocampo-Candiani, 2015). Mucosal lesions, characterized by erosion and desquamation, affect the conjunctival, oropharyngeal, nasal, esophageal, urethral, anal, vaginal, and perineal mucosa (Vieira et al., 2021). The lesions are painful and can cause complications such as urinary retention, blepharitis, conjunctival hyperemia, and purulent conjunctivitis (Vieira *et al.*, 2021).

As SJS/TEN progresses, complications arise due to the involvement of the respiratory, cardiovascular, gastrointestinal, and renal systems, with a mortality rate of around 70% (Sacoto, 2023). The lack of epidermal protection increases susceptibility to sepsis, the main cause of death in these patients (Martínez-Cabriales; Gómez-Flores and Ocampo-Candiani, 2015). Nephrotoxic cytokines involved in SJS/TEN, along with hypovolemia and decreased cardiac output, can cause kidney injury, such as electrolyte imbalances, prerenal azotemia, tubular necrosis, and acute renal failure. Lung involvement can result in bronchiolitis obliterans or diffuse interstitial pneumonitis (Martínez-Cabriales; Gómez-Flores and Ocampo-Candiani, 2015).

Diagnosing SJS is challenging due to its clinical similarity to other skin diseases in the early stages but is more beneficial when performed quickly (Caminha *et al.*, 2021). The diagnosis is based on clinical history and physical examination, with cutaneous and mucosal lesions characterized by erosion and desquamation, mainly in the oral, ocular, and genital mucosa. In 90% of cases, there is hemorrhagic and very painful involvement, affecting less than 10% of the body surface (Vieira *et al.*, 2021).

The initial evaluation includes checking vital signs, a complete blood count, arterial blood gas analysis, renal and liver function, C-reactive protein, plasma protein electrophoresis, and blood glucose. Skin biopsy for histopathological study, which reveals minimal inflammatory cell infiltrate with a predominance of CD4+ T lymphocytes, apoptotic keratinocytes, and epidermal detachment, is the only specific test (Dourado; Ribeiro, 2023). Laboratory and imaging tests are important to assess the patient's current state and perform the SCORTEN, a test used to determine the patient's prognosis (Torres; Olmos, 2013).

Differential diagnosis includes diseases causing cutaneous lesions, such as linear IgA dermatosis, bullous pemphigoid, and staphylococcal scalded skin syndrome. Histopathological study, direct immunofluorescence, serum antibody determination, and clinical history help differentiate (Roujeau, 2017). Erythema multiforme is also a differential, with a different evolution, starting with lesions on the backs of the hands and symmetrical involvement (Roujeau, 2017).

TREATMENT

The treatment of SJS is primarily based on identifying and suspending the triggering agent. Subsequently, it is crucial to choose a pharmacological therapy according to the severity of the disease and the patient's clinical conditions, individually (Campos; Cintra

and Ximenes, 2023). There are several systemic treatment options. For systemic treatment, drugs like cyclosporine, intravenous immunoglobulin (IVIG), corticosteroids, and tumor necrosis factor-alpha (TNF-α) inhibitors are used (Sacoto, 2023).

Corticosteroids are effective in treating SJS and TEN, especially in severe cases, when administered early, in pulse regimen, or in selected subgroups (Campos; Cintra; Ximenes, 2023). However, the use of corticosteroids in TEN remains controversial due to increased complications and mortality in some studies. Early, short-duration administration in moderate doses (prednisone 1 to 2 mg/kg for 3 to 5 days) may be beneficial, although a more recent review has not confirmed this effect (Estrella-Alonso *et al.*, 2017).

Cyclosporines have shown beneficial results in mortality, but studies are limited due to the small number of participants. The recommended doses are 4 mg/kg/day, orally, divided into two doses, lasting no more than four weeks. Cyclosporine is well tolerated in most patients and can stop disease progression and initiate reepithelialization 2 to 5 days after starting treatment (Estrella-Alonso *et al.,* 2017).

TNF-α inhibitors, such as etanercept and infliximab, have shown benefits in a small number of cases, but their effectiveness has yet to be demonstrated due to a lack of controlled studies (Estrella-Alonso *et al.*, 2017). Thalidomide, another TNF-α inhibitor, is not recommended due to significant teratogenic risk and lack of evidence of effectiveness (Roujeau, 2017).

Plasmapheresis can be used to remove drugs, their metabolites, and cytotoxic mediators from the blood. Although it has demonstrated beneficial effects in some studies, it is generally used in combination with other treatments, making it difficult to assess its isolated effectiveness (Estrella-Alonso *et al.*, 2017).

There are also topical treatment options, such as creams, lotions, and ointments, which can relieve symptoms, reduce inflammation, decrease the risk of infections, speed up recovery, and prevent serious complications. Petrolatum gauze dressings and silver biosynthetic dressings are also used to cover lesions, preserve granulation tissue, and prevent infections (Ximenes *et al.*, 2023).

Supportive measures are essential for treating SJS and TEN. It is necessary to keep the patient well-nourished and hydrated, maintain hemodynamic balance, and use antibiotic therapy when necessary to prevent secondary infections (Campos; Cintra; Ximenes, 2023). Patients with severe forms of the disease should be transferred to specialized units to prevent life-threatening complications. Management is multidisciplinary and includes multiorgan care, early diagnosis, and cessation of the offending medication (Sacoto, 2023). Psychological and emotional support is also important due to the high traumatic degree of the disease (Ximenes *et al.*, 2023).

Oral, genital, and cutaneous erosions require antiseptic treatment. Ocular lesions should be managed by a specialist, using artificial tears and antibiotic eye drops without corticosteroids. Individual lesions usually heal within 1 to 2 weeks unless secondary

infection occurs. Most patients recover without sequelae, although mucosal lesions can cause late complications, such as bleeding and narrowing of affected sites. Patients should avoid future exposure to the SJS-causing agent (Roujeau, 2017).

REFERENCES

CAMINHA, Irla Carvalho Chaves, *et al.* Necrólise epidérmica tóxica/síndrome de stevens johnson: como o diagnóstico precoce pode impactar no prognóstico. **Revista Científica Multidisciplinar**, v. 2, n. 9, p. e29747-e29747, 2021.

CAMPOS, Sabryna Silveira; CINTRA, Bruno Barreto; XIMENES, Renata Maria Visniewski. Intervenções terapêuticas para o tratamento sistêmico da Síndrome de Stevens-Johnson (SSJ) e Necrólise Epidérmica Tóxica (NET): Uma revisão integrativa. **Research, Society and Development**, v. 12, n. 11, p. e71121143488-e71121143488, 2023.

DEWI, Cinthia Christina. Tinjauan atas Stevens-Johnson Syndrome dan Toxic Epidermal Necrolysis. **Cermin Dunia Kedokteran**, v. 46, n. 7, p. 55-59, 2019.

DOURADO, Eduardo Souza; RIBEIRO, Rebecca Heidrich Thoen. SÍNDROME DE STEVENS-JOHNSON: UMA REVISÃO BIBLIOGRÁFICA. **Revista Científica Multidisciplinar**, v. 4, n. 6, p. e463339-e463339, 2023.

ESTRELLA-ALONSO, Alfonso, et al. Necrolisis epidérmica tóxica: un paradigma de enfermedad crítica. **Revista Brasileira de Terapia Intensiva**, v. 29, p. 499-508, 2017.

LEITE, Letícia dos Anjos; PAIVA, Lívia Vitória de Carvalho; MIRANDA, Thais Serralheiro; DOS SANTOS Anna Catarina Moreira. SÍNDROME DE STEVEN JOHNSON: UMA REVISÃO ABRANGENTE DAS MANIFESTAÇÕES CLÍNICAS E TERAPÊUTICAS. **Revista Contemporânea**, v. 4, n. 4, p. e3889-e3889, 2024.

MARTÍNEZ-CABRIALES, Sylvia Aide; GÓMEZ-FLORES, Minerva; OCAMPO-CANDIANI, Jorge. Actualidades en farmacodermias severas: síndrome de Stevens-Johnson (SSJ) y necrólisis epidérmica tóxica (NET). **Gac Med Mex**, v. 151, n. 6, p. 777-87, 2015.

RIBEIRO, Anaira Gonçalves de Almeida; RIBEIRO, Maria Cristina; BENITO, Linconl Agudo Oliveira. Síndrome de Stevens-Johnson (SSJ) em adultos: revisão sistemática. **Universitas: Ciências da Saúde**, v. 15, n. 2, p. 117-125, 2017.

ROUJEAU, J.-C. Eritema multiforme. **EMC-Dermatología**, v. 51, n. 3, p. 1-9, 2017.

SACOTO, Gabriela Maribel Macancela. Necrólisis epidérmica tóxica. **Dominio de las Ciencias**, v. 9, n. 4, p. 330-346, 2023.

TORRES, Mauricio; OLMOS, Édgar. Reacciones medicamentosas severas Síndrome Stevens Johnson y síndrome DRESS. **Acta Médica Colombiana**, v. 38, n. 2, p. 76-82, 2013.

VIEIRA, Natália Abreu Silva, *et al.* Síndrome de Stevens-Johnson: revisão integrativa. **Revista Sustinere**, v. 9, n. 1, p. 96-107, 2021.

XIMENES, Renata Maria Visniewski; CINTRAET, Bruno Barreto Cintra; CAMPOS, Sabryna Silveira; GALINDO, Layanne Liege Domingos. Bases do tratamento tópico na Necrólise Epidérmica Tóxica e Síndrome de Stevens-Johnson: Uma revisão científica. **Research, Society and Development**, v. 12, n. 9, p. e12012943293-e12012943293, 2023.