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Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis, A Review of Pathogenesis, Clinical Features, Diagnosis and Treatment

Martyna Rozenbajgier ^{1a}, Justyna Wójcik-Grudzień ^{2b}, Paulina Pawłowska ^{3c},
Alicja Ozga-Stachurska ^{3d}

a) rozenbajgier.martyna@gmail.com; <https://orcid.org/0000-0001-5165-9719>

b) justynawojcik455@gmail.com ; <https://orcid.org/0000-0001-7163-6784>

c) aozga1@gmail.com; <https://orcid.org/0000-0003-1291-905X>

d) paulina.piotrowska222@gmail.com ;<https://orcid.org/0000-0002-5516-952X>

¹⁾ 5 Wojskowy Szpital Kliniczny z Polikliniką SPZOZ w Krakowie

²⁾ Mazowiecki Szpital Specjalistyczny Sp. z o. o. w Radomiu

³⁾ Wojewódzki Szpital Specjalistyczny im. Stefana Kardynała Wyszyńskiego Samodzielny Publiczny Zakład Opieki Zdrowotnej w Lublinie

Corresponding author: Martyna Rozenbajgier

e-mail: rozenbajgie.martyna@gmail.com

ORCID: 0000-0001-5165-9719

ABSTRACT

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, acute conditions, potentially life-threatening, immune-mediated and often unpredictable.

Characteristic for SJS and TEN is acute necrosis of the epidermis and mucous membranes, caused by the extensive death of keratinocytes. These syndromes are considered hypersensitivity reactions. They are most often caused by drugs. There have also been reports of SJS / TEN being caused by infection,

SJS/TEN disease is very rare and due to its rarity there is no specific pharmaceutical algorithm. Supportive care and treatment of symptoms are very important. The most crucial part of non-pharmacologic treatment of SJS/TEN is the detection and cessation of the pharmaceutical that caused the disease.

The aim of this literature review was to summarize current knowledge about the pathogenesis, clinical features, diagnosis and treatment of Stevens- Johnson Syndrom and Toxic Epidermal Necrolysis.

Standard criteria were used to review the literature data. The search of articles in the PubMed and Google Scholar database was carried out using the following keywords: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, cutaneous adverse drug reactions

Key words: Stevens- Johnson Syndrome, Toxic Epidermal Necrolysis, cutaneous adverse drug reactions

INTRODUCTION

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, acute conditions, potentially life-threatening, immune-mediated and often unpredictable. Most of the reported cases of SJS and TEN have been drug-induced. The annual incidence of TEN and SJS is 0.4-1.2 and 1.2-6 cases per million, respectively [1]. These syndromes more often affect women (1.5: 1) and the elderly [2]. Some patients are genetically predisposed to developing the disease [3]. The risk of developing SJS and TEN in HIV patients and AIDS patients is about a thousand times higher than in the general population [4].

Characteristic for SJS and TEN is acute necrosis of the epidermis and mucous membranes, caused by the extensive death of keratinocytes. It causes the separation of the epidermis from the skin at the point of contact [5]. Most experts believe that SJS and TEN are a spectrum of the same disease entity but with different severity of symptoms, of which TEN is the more severe form of the disease. They are distinguished on the basis of the percentage of skin affected [6].

Diagnosis Based on BSA (%)	
SJS	<10%
SJS/TEN Overlap	10-30%
TEN	>30%

Table 1. Differentiation of SJS and TEN based on the occupied body surface area (%) [7].

AIM OF THE STUDY

The aim of this literature review was to summarize current knowledge about the pathogenesis, clinical features, diagnosis and treatment of Stevens- Johnson Syndrom and Toxic Epidermal Necrolysis.

MATERIAL AND METHODS

Standard criteria were used to review the literature data. The search of articles in the PubMed and Google Scholar database was carried out using the following keywords: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, cutaneous adverse drug reactions

DESCRIPTION OF THE STATE OF KNOWLEDGE

Pathogenesis

and

pathophysiology

Drugs are the most common cause of SJS, while TEN is caused almost entirely by drugs.

Common Drug Triggers of SJS/TEN

Anti-epileptics	Antibiotics
○ Lamotrigine	○ TMP-SMX
○ Phenytoin	○ Aminopenicillins
○ Carbamazepine	○ Tetracyclines
○ Valproic Acid	○ Cephalosporins
○ Phenobarbital	Immune Checkpoint Inhibitors
NSAIDs	○ Nivolumab
Allopurinol	○ Pembrolizumab
Nevirapine	

Table 2. Drugs that are the most common causes of SJS / TEN. [7]

Infections are suspected to be another possible trigger of SJS / TEN. So far, the relationship with the occurrence of these disease syndromes has been best documented for *Mycoplasma pneumoniae* [6].

About 15-30% of the cause is unknown [7]. Despite the knowledge of the causes of some SJS / TEN cases, the exact pathophysiology of the syndromes has not been fully understood so far. According to one theory, apoptosis is induced or the products of drug metabolism accumulate [8].

Type IV hypersensitivity reactions and mediated by T lymphocytes are also assumed to be involved. Some hypotheses assume the concept of hapten / pro-hapten, pharmacological interaction (pi) and the concept of an altered peptide [9, 10].

Certain HLA subtypes have been shown to be associated with a higher risk of SJS / TEN or an increased risk of adverse reactions after taking certain medications. A study published in 2016 by Shih-Chi Su et al., In which a total of 155 serum samples were tested for the level of 28 different chemokines and cytokines, showed that granulysin and IL-5 are strongly associated with the severity of the disease [11].

Clinical features

Patients often report prodromal symptoms before developing SJS / TEM cutaneous symptoms. They appear about 48-72 hours before the cutaneous manifestation of the disease and are manifested by increased body temperature, cough, pain in the muscles and throat [12]. After the prodromal symptoms stage, the skin and mucous membranes are involved. Appearance of resembling spots, warmed, initially on the trunk and then fusing together and forming blisters with a positive

Nikolsky symptom, consisting in the creaking of the epidermis as a result of rubbing the skin or mucosa. The process of evolving of skin changes may take several hours or even several days.

Mucosal lesions usually cover two or more mucosal surfaces and may occur before or after skin lesions [13]. They begin with a mucosal rash and swelling, progressing to erosions on the genitals, eyes, mouth, in the throat and upper respiratory tract. Early ophthalmological consultation is important to prevent permanent visual impairment [14]. Ocular manifestations may include corneal ulceration, eyeballitis, and choroiditis. There are also changes in the urinary system, genital tract and digestive tract, and they are not rare.

The loss of functionality of the epidermal barrier may contribute to the development of bacterial infections, thermoregulation disorders and increased water loss through the body integuments, which may lead to dehydration and electrolyte disturbances [14].

Diagnosis

Establishing the diagnosis of SJS / TEN is based on the clinical picture. A well-collected history, including information about recently taken drugs and infections, as well as a physical examination, is extremely important.

Blood, skin, and urine cultures may reveal an infectious cause. It is also possible to perform a skin biopsy with subsequent immunofluorescence for the differential diagnosis of other diseases with a similar clinical picture, such as: staphylococcal scalded skin syndrome, acute generalized exanthematous pustulosis, acute severe graft-versus-host disease and paraneoplastic pemphigus [7]

TREATMENT

SJS/TEN disease is very rare and due to its rarity there is no specific pharmaceutical algorithm. The most important still seems to be the supportive care and treatment of symptoms.

The most important part of non-pharmacologic treatment of SJS/TEN is the detection and cessation of the pharmaceutical that caused the disease [15]. Next steps include fluid management, controlling of the infection and taking care of wounds. Patients with SJS/TEN have similar requirements to burn patients, but they need 30% less of fluids than them [16]. Similarly to burn patients, skin of SJS/TEN patients has a disrupted thermoregulatory function, thus the environment in which patients stay should be warm [17]. Also, patients should be given enteral feed [18].

What is more, it is crucial to prevent infection by maintaining hygienic environment. It is obtained by sterile handling of wounds. It was proved that there is no great influence of antibiotic therapy in SJS/TEN cases [19].

There is also a controversial non-pharmaceutical way of SJS/TEN treatment – surgical debridement. However, the choice of this way of treatment depends on the place and hospital from where the patient receives help. A study [20] was composed of 40 patients suffering from SJS/TEN. They were all treated aggressively with symptomatic treatment, then they underwent surgical debridement of wounds; subsequently, wounds were covered with antimicrobial dressing; patients also received IVIg. Finally, the mortality rate reported was only 10%, much lower than predicted (16.7%). There is also an alternative to surgical debridement – anti-shear therapy [21] In this kind of treatment, fluid from the blisters is taken, then denuded epidermis remains left, acting like a skin graft. All in all, there are no strong evidences for these two therapies to be effective.

As it was mentioned, the data about pharmacological way of SJS/TEN treatment is limited and there are no specific therapies, because the disease is very rare. There are some studies [22] considering the

role of TNF-alpha inhibitors as they can cause immunosuppression. One of them displayed a slight improvement in mortality rate [23].

It is still not known what is the role of corticosteroids in monotherapy in SJS/TEN management. Some studies [24] showed an insignificant effect; other [25] showed no improvement, as well as researches [26] about the IVIg in monotherapy. However, the treatment composed of them both (corticosteroids and IVIg) seems to be effective [27]. and to slightly reduce mortality rate.

There are also some promising ways of treatment such as cyclosporine, that was effective in some researches [28, 29, 30]. However, it still needs further research.

SUMMARY

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis are a serious and severe diseases that can be a threat to human life. The key is to quickly establish a diagnosis, which is mainly based on the symptoms presented by the patient and a carefully conducted medical history. It is also important to identify the causative agent of the disease and discontinue it as soon as possible.

Data about pharmacological way of SJS/TEN treatment is limited and there are no specific therapies, because the disease is very rare. It is crucial to prevent infection by maintaining hygienic environment. It is obtained by sterile handling of wounds.

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