

CASE REPORT AND MINIREVIEW

STEVENS-JOHNSON SYNDROME IN A CHILD: CASE REPORT AND MINIREVIEW

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ABSTRACT

Introduction. Stevens-Johnson syndrome is a rare, severe and life-threatening condition that develops mostly in response to drug use.

Case presentation. We present a case of Stevens-Johnson syndrome in a boy of 11 years old, most probably developed in response to a combination of etiologic factors, such as virus infection, use of ibuprofen, and topical use of sulfanilamide agents. The clinical picture of the child was suggestive, involving tunica mucosa of mouth, genitals, conjunctiva, and skin. Parenteral administration of glucocorticoids, detoxification, antibiotic prophylaxis, and topical treatment led to rapid regression of clinical symptoms and prevented the development of complications.

Conclusions. The treatment of Stevens-Johnson syndrome involves systemic glucocorticoids in combination with topical therapy. In our patient, the treatment avoided serious complications and led to rapid regression of cutaneous manifestations. The etiology of Stevens-Johnson syndrome is sometimes difficult to establish. Physicians should avoid polypragmasia and

RÉSUMÉ

Le syndrome de Stevens-Johnson chez un enfant : rapport du cas et mini-revue

Introduction. Le syndrome de Stevens-Johnson est une maladie rare, grave et potentiellement mortelle qui se développe le plus souvent comme une réponse à la consommation de drogues.

Rapport du cas. L'article présente un cas clinique de syndrome de Stevens-Johnson chez un garçon de 11 ans qui s'est probablement développé comme une réponse à une combinaison de facteurs étiologiques tels qu'une infection virale, l'utilisation d'ibuprofène et l'utilisation locale d'agents sulfanilamides. Le tableau clinique de l'enfant était suggestif des lésions de la muqueuse buccale, des organes génitaux, de la conjonctive et de la peau. L'administration parentérale de glucocorticoïdes ainsi que la detoxification, la prophylaxie antibiotique et le traitement local ont conduit à une régression rapide des symptômes cliniques et ont empêché le développement de complications.

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unreasonable prescription of drugs and be aware of the risk of Stevens-Johnson syndrome, especially in pediatric patients.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, glucocorticoids, side effects of drugs.

List of abbreviations:

CsA – cyclosporin
 DIC – disseminated intravascular coagulation
 ESR – erythrocyte sedimentation rate
 Hb – hemoglobin
 Iv Ig – intravenous immunoglobulins
 SJS – Stevens-Johnson syndrome
 TEN – toxic epidermal necrolysis

INTRODUCTION

Despite their positive therapeutic effects, the use of drugs can cause various adverse reactions: from mild reactions to severe, life-threatening, such as anaphylactic shock, Stevens-Johnson and Lyell syndromes, Ray syndrome and others^{1,4}.

Stevens-Johnson Syndrome (SJS) is a rare, potentially life-threatening, severe mucosal hypersensitivity reaction of a delayed type, characterized by epidermal detachment, mucosal erosion, and severe systemic symptoms requiring immediate medical intervention^{1,3}. Although in 74-94% of cases SJS is associated with adverse drug reactions and response to infection, the etiology of this pathological process is complex and not fully understood^{3,5,6}. Due to the severity of these reactions, early recognition, diagnosis, treatment, and the development of preventive agents are important for improving clinical outcomes⁷. Therefore, information on clinical cases of such rare pathological conditions is extremely important.

CASE PRESENTATION

A 11-year-old boy was admitted to the Ternopil Regional Children's Hospital, Ukraine, with complaints of fever up to 39.9°C, bullous lesions up to 2 cm in diameter on the trunk, face, ears, genitals, swelling and erosion in the lip area, burning sensation in the eyes and oral cavity, difficult swallowing, general weakness. From the history, moderate swelling of the lips appeared 4 days before the occurrence of these complaints. Without medical examination, the parents treated the lips with streptocide powder, as a few months ago a streptocide was prescribed by a doctor when such symptoms occurred. Before that, according to the parents' report, the child suffered from a mild acute respiratory viral infection,

Conclusion. Le traitement du syndrome de Stevens-Johnson implique des glucocorticoïdes systémiques en combinaison avec une thérapie topique. Chez notre patient, le traitement a évité de graves complications et a entraîné une régression rapide des manifestations cutanées. L'étiologie du syndrome de Stevens-Johnson est parfois difficile à établir. Les médecins doivent éviter la polypragmasie et la prescription déraisonnable de médicaments et être conscients du risque du syndrome de Stevens-Johnson, en particulier chez les patients pédiatriques.

Mots-clés: syndrome de Stevens-Johnson, nécrolyse épidermique toxique, glucocorticoïdes, effets secondaires aux médicaments.

manifested by cold, lacrimation, fever up to 37.5°C. To reduce the body temperature, ibuprofen was used. After that, the catarrhal signs disappeared, but moderate swelling of the lips appeared. After 3 days, the



Figure 1. Elements of a rash on the right upper extremity of a child with Stevens-Johnson syndrome.

child had a rash all over the body and on the mucous membranes of the mouth and eyes, odynophagia, fever up to 39.9°C.

The clinical examination revealed the presence of bullae up to 2 cm in diameter on the trunk, face, upper extremities, ears, penis, erosions, and epithelization sites in some places after epidermal detachment (Fig. 1, 2, 3). The mucous membranes of the lips and oral cavity were covered with erosions and

hemorrhagic crusts. The conjunctiva was dry, hyperemic. The lung and heart sounds were normal, heart rate 92 beats/min.

The blood tests revealed anemia (Hb 10.6 g/dL), mild leukocytosis (10,560/ μ l), transient lymphopenia (636/ μ l, moderate hypoproteinemia (53.6 g/L). The child was hospitalized in the intensive care unit of the hospital.



Figure 2. Elements of a rash on a child's body with Stevens-Johnson syndrome.



Figure 3. Elements of a rash on a child's face with Stevens-Johnson syndrome.

Considering the characteristic clinical features, SJS was diagnosed and treatment with intravenous systemic glucocorticoids at 10 mg/kg/day (prednisone, dexamethasone) was initiated, together with broad-spectrum antibiotics, antihistamines, sodium thiosulfate, local skin treatment with povidone-iodine and furacillin, oral mucosa treatment with quercetin ointment, eyes treatment with hydrocortisone ointment, enterosorbents, detoxification therapy, hygienic care of skin and mucous membranes, adherence to aseptic conditions of stay of the patient in a ward (frequent ventilation, quartz, daily change of clothes and bed linen of the patient). In the dynamics of treatment, the condition of the sick child improved, during the first 2 days of treatment only a few new bullous elements appeared in the area of the ears, there were no other new rashes. Gradually, on the background of treatment, the bullous elements disappeared with the onset of epithelization, with no signs of suppuration. The child was discharged from the hospital after 19 days, in a good clinical condition.

DISCUSSION AND REVIEW OF THE LITERATURE

For long, the SJS was regarded as an extremely difficult version of multiform erythema, known for more than 140 years. The first reports of SJS were published by Hebra in 1866⁸. SJS was first described by two pediatricians (Stevens and Johnson) in New York City in 1922, in two children⁹. In 1956, Lyell used the term «toxic epidermal necrolysis» (TEN) to describe skin lesions in four of his patients, based on the belief that these lesions were induced by circulating toxin¹⁰. TEN was also described separately by Lang and Walker in 1956¹¹.

SJS and TEN are considered to be one disease with varying degrees of severity^{12,13}. The main criteria for the current classification of SJS-TEN is the size of the area of the epidermal detachment relative to the total surface of the patient's body (in percentage). Accordingly, there are three clinical types^{8,14}:

1. SJS («small form of TEN») – epidermis detachment no more than 10% of the body surface.
2. The intercurrent or transitional form of SJS-TEN (overlapping SJS-TEN) – an epidermal detachment from 10 to 30% of the body surface.
3. TEN – detachment of the epidermis more than 30% of the body surface.

SJS-TEN is a very rare disease. This syndrome occurs at any age, mainly in people 20-40 year-old. The disease is observed very rarely in children in the first 3 years of life. The overall incidence of SJS-TEN ranges from 0.4-1.2 to 12.7 cases per 1 million inhabitants per year^{3,7,8,12}, depending on the patient's region of residence, of which approximately 20% are

pediatric cases. Mortality of SJS ranges from 1% to 4%, whereas of TEN it increases to 25-35%^{12,15} and even to 44-50%³.

Data on the ratio of men and women are controversial. Most researchers note a higher prevalence of disease in men. The disease is characterized by seasonality, the incidence of SJS-TEN is usually recorded in winter and early spring⁸.

The etiology of SJS-TEN in children does not differ significantly from adults¹.

There are 4 main causes for the development of SJS-TEN:

- drugs;
- infections;
- malignant diseases;
- not established (idiopathic SJS-TEN)⁸.

Most cases of SJS and TEN in children and adults are caused by drugs. Although any drug can cause SJS/TEN, most reactions can be attributed to a group of high-risk drugs¹. In the development of drug-induced SJS-TEN, the most incriminated are antibacterials, especially antibiotics (penicillins, macrolides, fluoroquinolones, chloramphenicol) (up to 55%) and sulfanilamides (co-trimoxazole) (up to 10%), antifungal agents (imidazole), non-steroidal anti-inflammatory agents (especially ibuprofen, indomethacin, piroxicam, acetylsalicylic acid) (up to 25%), anticonvulsants (phenobarbital, phenytoin, carbamazepine, lamotrigine, valproic acid), allopurinol, vitamins, local anesthetics, vaccines. Rarely, topical and systemic glucocorticosteroids can be the cause^{8,11,16}.

Sulfanilamides, penicillins, non-steroidal anti-inflammatory drugs, and anticonvulsants are more common involved in pediatrics with SJS/TEN induced by drugs, due to their more frequent use in children^{1,17}.

In children, SJS-TEN is often triggered by infections. *Mycoplasma pneumoniae* and cytomegalovirus infections are the most common pathogens of SJS/TEN, especially in children^{1,18}. Among the infectious agents are viruses (herpes simplex virus type I and type II, adenovirus, Coxsackie B5 virus, etc), bacteria (*Proteus*, *Salmonella*, β -hemolytic streptococcus group A, tuberculosis, etc), fungi (causative agents of coccidioides immitis, dermatophytosis, histoplasmosis). The participation of protozoa (pathogens of trichomoniasis and malaria) is also possible⁸. More than half of SJS cases in children develop on the background of upper respiratory tract infections⁸.

SJS-TEN can be associated with autoimmune, immunodeficiency and malignant diseases, among the latter, carcinomas and lymphomas playing a leading role^{19,20}. It is possible to combine several etiological factors (infection, drugs, malignancies). It should be noted that in many cases the specific etiological factor

of SJS-TEN can not be identified. According to the literature, 25-50% of cases of SJS-TEN are idiopathic⁸.

In our clinical case, a possible cause of the development of SJS was the combination of the infectious factor, the use of ibuprofen and the sulfanilamide drug streptocide, in particular its local use. The etiology of the SJS in this child has not been established accurately.

Although the exact pathogenesis of SJS/TEN remains uncertain, specific agents (for example, drugs, infections) are thought to elicit an immune-mediated cytotoxic response against keratinocytes, triggering their apoptosis. The major cytotoxic molecules involved in this mechanism are granulysin, perforin/granzyme B and the ligand Fas – Fas ligand. Most studies suggest that granulysin is the most potent inducer of the disease. Studies have shown that the concentration of granulysin in the patient's blisters correlates with the severity of the disease⁵. Many CD8⁺ T-cells and other cytotoxic cells (NK, NKT) are identified within the skin lesions. Other inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ), interleukin-15 (IL-15), have also been found to be involved in SJS/TEN immune responses⁷. More recently, the role of T-helper cells in the pathogenesis of SJS/TEN, as enhancers of the immune response in affected patients, has been proposed. Also, many reports have linked some HLA genes to the frequency of SJS/TEN, due to the effects of specific drugs, such as carbamazepine and allopurinol^{12,21,22}. Despite various initial mechanisms of the pathological process induction, ultimately activated lymphocytes induce apoptosis in keratinocytes throughout the depth of the dermis, leading to painful blisters and disruption of the skin and mucous membranes^{5,11}.

Initial symptoms include fever, conjunctivitis, cough, arthralgia, myalgia, rhinitis, headache, anorexia, nausea, and vomiting, with or without diarrhea¹¹. The prodromal period lasts 2-3 days, sometimes up to 10-11 days¹¹. Conjunctivitis usually occurs 1-3 days before skin lesions¹¹. Often, the initial signs of the disease are quite similar to those of an acute respiratory disease. In our case, there were no such prodromal symptoms, excepting the swelling of the mucous membrane of the lips. The next sign is the detachment of the mucous membranes (oropharyngeal, conjunctival, anogenital and nasal)¹. The mucosa is injured in 90% of SJS cases^{11,23}. Usually, more than two mucous membranes are involved, most often conjunctiva and oral mucous membranes¹¹. Patients with involvement of the mucous membrane of the urogenital tract complain of dysuria or inability to urinate⁸. Our patient had a classic lesion of the oral mucosa, conjunctiva, and penis mucosa.

Skin lesions usually begin as erythematous macula, with the possibility of rapid development into papules and bullous elements¹². In the vast majority of patients, the cutaneous lesions are accompanied by fever, which is rapidly disappearing⁸, as in our patient. The rash spreads symmetrically, mainly on the trunk and proximal extremities, within an hour to 2-3 days¹. Bullous lesion of the skin is characterized by peeling of the epidermis and formation of major erosions, as a result of the merger and rupture of the blister. Bullous rash on the skin is usually combined with erythematous and hemorrhagic spots⁸. The large loss of the epidermis layer leads to infections, electrolytes imbalances, and in some cases organ failure, which can lead to death^{12,24}. Epithelization begins several days after cessation of the disease and usually ends after about 3 weeks, excepting mucous membranes and pressure sites, that take longer¹¹.

SJS/TEN may also have extracorporeal manifestations, such as respiratory, renal, hepatic, and gastrointestinal lesions during the acute stage^{7,25,26}.

Among the complications of SJS/TEN there are the following:

- infectious complications, sepsis^{1,8,11};
- hypopharyngeal stenosis, in combination with dysphagia and esophageal strictures¹;
- pneumonitis, lung atelectasis, and pneumothorax^{11,27};
- acute renal failure, bladder bleeding, balanoposthitis, urethral strictures in boys, vulvovaginitis, vaginal stenosis, chronic genital erosion⁸;
- encephalopathy, myocarditis, etc²⁸.

The diagnosis of SJS is based on the clinical picture of the disease and paraclinical tests, that include:

- Hemogram (characteristic leukocytosis with a shift of the leukocyte formula to the left and increased ESR, absence of elevated blood eosinophil level)¹⁶;
- Liver and kidney function tests;
- Blood electrolytes;
- Blood sugar;
- General analysis and microscopy of urine;
- Chest X-ray (as indicated)¹.

Recommended studies for all patients are designed to assess the extent of damage to different organ systems, to predict and plan further treatment^{1,12}. It should be noted that the severity of systemic lesions does not necessarily correlate with epidermal necrolysis¹. Histological examination is not specific. Skin biopsy and immunofluorescence may be required in special situations for differential diagnosis¹¹.

With the established cause of SJS-TEN, it is necessary to stop the further influence of the etiological factor, to cancel the drug involved (level of evidence II, degree of recommendation B)^{1,8}. Considering the severity and life-threatening nature of SJS/TEN, it is

logical to discontinue any medication the patient is taking. However, if medication is absolutely necessary (especially relevant for epileptics and severe life-threatening infections, such as septicemia), these drugs may be replaced by structurally unrelated drugs. It is important to limit medication to the lowest possible¹.

General approaches of SJS-TEN therapy are similar to those in thermal burns. However, the thermal burn lasts for a short period (several seconds) and SJS-TEN progresses within a few days after hospitalization. Also, skin necrosis in burns is often more profound than in SJS-TEN, although the area of skin damage in both cases can be considerable.

The basic principles of care and treatment of patients with SJS-TEN are:

- careful general care of the patient and strict adherence to the rules of asepsis, creation of a sterile microenvironment;
- constant temperature control in the ward;
- avoidance of any adhesive materials (bandages, gauze, napkins, etc) in the care of the skin and mucous membranes during the evolution of the disease;
- providing stable access to a peripheral vein outside the lesion area;
- organization of early enteral nutrition;
- specific (immunomodulatory) therapy (systemic corticosteroids, cyclosporine, intravenous immunoglobulin, cyclophosphamide, plasmapheresis, and tumor necrosis factor inhibitors);
- anticoagulant therapy (prevention of DIC and thromboembolism);
- correction of hydro-electrolyte disturbances;
- drug control of pain, symptomatic therapy⁸.

Ideal therapy is still a matter of debate, as there is only a limited amount of good quality research comparing the utility of different specific therapies¹. Commonly used treatments worldwide include intravenous immunoglobulins (Iv Ig) and systemic corticosteroids. Recently, cyclosporin (CsA) and tumor necrosis factor- α (TNF- α) inhibitors have also been investigated^{12,29}.

There is a debate on the efficacy and feasibility of using glucocorticosteroids (level of evidence II, degree of recommendation B) in SJS⁸. Despite the discussion, systemic corticosteroids remain the mainstay of therapy for SJS and TEN. The rationale is that both diseases are immunity-mediated processes, and corticosteroids inhibit the intensity of the reaction, prevent/reduce skin necrolysis, reduce the synthesis of proinflammatory molecules, and inhibit the production of prostaglandin and leukocyturia, impair the function of monocytes and lymphocytes, reduce fever and discomfort, and prevent internal organ damage in an early stage^{1,12}. Specialists in the field

of pediatrics do not deny the possibility of the use of steroid hormones, especially in the severe course of SJS, carefully concluding that the early appointment of a short course of glucocorticoid may even stop the progression of the process^{1,8}. Our patient used glucocorticoid pulse therapy, which promptly regressed the pathological process and avoided the development of complications. Therefore, in our opinion, the use of glucocorticoids is quite effective, particularly in pediatric patients.

The results of using intravenous immunoglobulin (Iv Ig) for the treatment of SJS are also quite divergent¹. A systematic review did not show a statistically significant difference in outcomes in patients receiving systemic steroids compared with intravenous Ig^{12,30}.

Cyclosporine (CsA) has also shown promising results in the treatment of pediatric patients with SJS and TEN^{1,31}. In fact, CsA is a potent immunosuppressive and immunomodulatory drug that affects mainly T-cell-dependent immune mechanisms, through inhibition of T-helper cells and cytotoxic T-cells. It also inhibits the release of interleukin (IL)-3, IL-4, IL-5, interferon-gamma, granulocyte monocyte colony-stimulating factor and TNF- α ³². Although CsA may have a potential role in the treatment of pediatric patients with SJS/TEN, experience with this drug is rather limited and needs further study¹².

Although the role of plasmapheresis/hemoperfusion in the treatment of pediatric SJS/TEN has not been well established, it may be of potential benefit mainly in patients with severe disease (predominantly TEN) or those who have not responded to other treatments (corticosteroids and/ or Iv Ig)^{12,33}. Tumor necrosis factor- α inhibitors (etanercept, infliximab, and rituximab) are currently used to treat a wide range of autoimmune and inflammatory conditions¹², including SJS. While the results seem encouraging, they should be used with caution because of the possible side effects (increased risk of infection, hematologic complications, lymphoma development, hepatotoxicity) and a fairly high cost of treatment³⁴. Other drugs with anti-TNF- α properties (N-acetylcysteine and pentoxifylline) are also used, but the literature on their efficacy is scarce^{12,24,30}.

An intravenously 30% sodium thiosulphate solution of 10 ml every day is also often used as an anti-inflammatory, antitoxic and anti-allergic agent, as well as in our patient. Prophylactic antibacterial therapy is intended to prevent the development of bacteremia in the presence of a significant amount of damaged skin and mucous membranes, prolonged fever and signs of secondary infection of the rash elements. Preference is given to cephalosporins of III

and IV generations, fluoroquinolones or aminoglycosides. The use of penicillin antibiotics is not recommended¹⁶.

Skin treatment tactics in patients with SJS are similar to those in burns. In the case of the exudative component, the skin should be dried and disinfected with saline solutions, 3% hydrogen peroxide solution, aniline dye solutions, chlorhexidine, povidone iodine solution, furacillin and others. As the epithelization appears, solutions can gradually be replaced with creams and ointments. Topical glucocorticosteroids are most commonly used for this purpose. In case of secondary infection, combined topical therapy is used. In the period of residual desquamation of the epidermis, it is recommended to use neutral skin moisturizers (gels, creams)^{16,33}. In our case, we used skin treatment with a solution of povidone iodine and furacillin, with a good result.

In case of lesions of the mucous membranes of the eyes, the treatment should be carried out 5-6 times a day with the use of eye gels, drops, with severe manifestations – glucocorticosteroid and antibacterial eye ointments. Treatment of the oral mucosa is performed after each meal (disinfectant, saline solution), urinary system (disinfectant solution) – 3-4 times a day and after each urination¹⁶.

The patient who has undergone an SJS is monitored by the allergist for a year. Adherence to a hypoallergenic diet is recommended. For prophylactic purposes, after discharge from the hospital, it is recommended to prescribe 3rd generation antihistamines for 3-4 weeks¹⁶.

The patient was issued a memo, indicating illicit drugs (in the case of drug-induced SJS) and teaching the child and parents the correct algorithm of emergency care in the case of allergic reactions, the technique of drugs injection in the case of repeated contact with the allergen and the emergence of acute toxic allergies. The most important is the rational use of drugs, only by the prescription of a doctor, avoiding polypragmasy.

CONCLUSIONS

Stevens-Johnson syndrome is a severe pathological condition caused in most cases by drugs and infectious agents. The treatment of Stevens-Johnson syndrome involves systemic glucocorticoids in combination with topical therapy. In our opinion, it is optimal to use glucocorticoid pulse therapy, antibiotic therapy and topical treatment, which help to stabilize the child's condition and prevent the further manifestation of the disease and development of complications. The etiology of Stevens-Johnson syndrome is sometimes difficult to establish. Physicians should

avoid polypragmasy and unreasonable prescription of drugs and be aware of the possibility of developing Stevens-Johnson syndrome, especially in pediatric patients.

Author Contributions:

I.C., O.B. were responsible for the diagnostic procedures, clinical diagnosis, and treatment decisions. I.C. and A.C. wrote the manuscript. A.C., I.C., and N.Y. were responsible for the data acquisition. O.B. I.B. and U.M. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed to the published version of the manuscript.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article“

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study“

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REFERENCES

1. Gupta LK, Martin AM, Agarwal N, et al. Guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis: An Indian perspective. *Indian J Dermatol Venereol Leprol.* 2016;82:603-25
2. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, et al. Current perspectives on Stevens-Johnson syndrome and toxic epidermal necrolysis. *Clin Rev Allergy Immunol.* 2018;54:147-76.
3. Shi T, Chen H, Huang L, Fan H, Yang D, Zhang D, Lu G. Fatal pediatric Stevens-Johnson syndrome/toxic epidermal necrolysis: Three case reports. *Medicine.* 2020;99:12(e19431).
4. Chornomydz I, Boyarchuk O, Chornomydz A. Reye (Ray's) syndrome: a problem everyone should remember. *Georgian Med News.* 2017;(272):110-118.
5. Davis WD, Schafer PA. Stevens-Johnson syndrome. A challenging diagnosis. *Advanced Emergency Nursing Journal.* 2018;40(3):176-182.
6. Dunn J. Genetics and Stevens-Johnson syndrome/toxic epidermal necrolysis: what have we learned? *JAMA Ophthalmology.* 2017;135(4):361-362.
7. Lin CC, Chen CB, Wang CW, Hung SI, Chung WH. Stevens-Johnson syndrome and toxic epidermal necrolysis: risk factors, causality assessment and potential prevention strategies. *Expert Review of Clinical Immunology.* 2020. DOI: 10.1080/1744666X.2020.1740591

8. Hebra F, Kaposi M. Diseases of the Skin, vol. 1. *New Sydenham Society, London*, 1866, 285.
9. Lyell A. Toxic epidermal necrolysis: an eruption resembling scalding of the skin. *Brit J Dermatol*. 1956;68:355
10. Lang R, Walker J. An atypical fatal bullous eruption of unknown aetiology. *S African M J*. 1956;30:97.
11. Del Pozzo-Magaña BR, Lazo-Langner A. Stevens-Johnson Syndrome and toxic epidermal necrolysis in children: a literature review of current treatments. *EMJ Dermatol*. 2016;4(1):83-89.
12. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol*. 1993;129(1):92-6.
13. Sharma VK, Jerajani HR, Srinivas CR, Valia A, Khandpur S. IADVL Consensus Guidelines 2006: Management of Stevens-Johnson syndrome and toxic epidermal necrolysis. In: Sharma VK, editor. Guidelines for vitiligo, Stevens-Johnson syndrome, toxic epidermal necrolysis and psoriasis. 2nd ed. New Delhi: IADVL's Therapeutic Guidelines Committee; 2008.
14. Roujeau JC. Epidermal necrolysis (Stevens-Johnson syndrome and toxic epidermal necrolysis): Historical considerations. *Dermatol Sin*. 2013;31(4):169-74.
15. Hallgren J, Tengvall-Linder M, Persson M. Stevens-Johnson syndrome associated with ciprofloxacin: A review of adverse cutaneous events reported in Sweden as associated with this drug. *J Amer Acad Derm*. 2003;49(5 Suppl):S267-9.
16. Forman R, Koren G, Shear NH. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in children: A review of 10 years' experience. *Drug Saf*. 2002;25(13):965-72.
17. Wetter DA, Camilleri MJ. Clinical, etiologic, and histopathologic features of Stevens-Johnson syndrome during an 8-year period at Mayo Clinic. *Mayo Clin Proc*. 2010;85(2):131-8.
18. Boyarchuk O. Allergic manifestations of primary immunodeficiency diseases and its treatment approaches. *Asian J Pharm Clin Res*. 2018;11(11):83-90.
19. Boyarchuk O, Balatska N, Chornomydz I. Evaluation of warning signs of primary immunodeficiencies. *Pediatrics Polska – Polish Journal of Paediatrics*. 2019;94(6):337-341.
20. Roujeau JC. Epidermal necrolysis (Stevens-Johnson syndrome and toxic epidermal necrolysis): Historical considerations. *Dermatol Sin*. 2013;31(4):169-74.
21. Amstutz U, Ross CJ, Castro-Pastrana LI, et al. HLA-A 31:01 and HLA-B 15:02 as genetic markers for carbamazepine hypersensitivity in children. *Clin Pharmacol Ther*. 2013;94(1):142-9.
22. Creamer D, Walsh SA, Dziejewski P, et al. U.K. Guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. *Br J Dermatol* 2016;174(6):1194-227.
23. Martínez-Cabrales SA, Gómez-Flores M, Ocampo-Candiani J. News in severe clinical adverse drug reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). *Gac Med Mex*. 2015;151(6):777-87.
24. Sugino K, Hebisawa A, Uekusa T, Hatanaka K, Abe H, Homma S. Bronchiolitis obliterans associated with Stevens-Johnson Syndrome: histopathological bronchial reconstruction of the whole lung and immunohistochemical study. *Diagnostic Pathology*. 2013;8(1):134.
25. Jha AK SA, Jha RK, Raj VK. Spectrum of gastrointestinal involvement in Stevens-Johnson syndrome. *World Journal of Gastrointestinal Endoscopy*. 2019;11(2):115-123.
26. Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *Arch Dis Child* 2013;98(12):998-1003.
27. Abe R, Shimizu T, Shibaki A, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome are induced by soluble fas ligand. *Am J Pathol* 2003;162(5):1515-20.
28. Curtis JA, Christensen LC, Paine AR, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis treatments: An Internet survey. *J Am Acad Dermatol*. 2016;74(2):379-80.
29. Del Pozzo-Magana BR, Lazo-Langner A, Carleton B, et al. A systematic review of treatment of drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *J Popul Ther Clin Pharmacol*. 2011;18:e121-33.
30. Koh MJ, Tay YK. An update on Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *Curr Opin Pediatr* 2009;21(4):505-10.
31. Durnian JM, Stewart RM, Tatham R, Batterbury M, Kaye SB. Cyclosporin A-associated malignancy. *Clin Ophthalmol*. 2007;1(4):421-30.
32. Hinc-Kasprzyk J, Polak-Krzeminska A, Glowacka M, Ozog-Zabolska I. The use of plasmapheresis in a 4-year-old boy with toxic epidermal necrosis. *Anaesthesiol Intensive Ther*. 2015;47(3):210-3.
33. Zhernosek VF, Dyubkova TP. Stevens-Johnson syndrome – toxic epidermal necrolysis in children. Part I. Part II. System, local treatment. *Pediatric Pharmacology*. 2011;8(2):22-26.
34. Diaconu CC, Dediu GN, Iancu MA. Drug-induced arterial hypertension, a frequently ignored cause of secondary hypertension: a review. *Acta Cardiologica*. 2018;73(6):511-517.