

# Steven-Johnson Syndrome in Child

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*Steven-Johnson Syndrome and NET (toxic epidermal necrolysis), different expressions of the same condition were named according to the percentage of affected skin: <10% in Steven-Johnson Syndrome and >30% in NET. Small ages may be a target for these rare diseases, in direct relation to drug abuse (antibiotics, NSAIDs, antiepileptics, etc.). Survival depends on the rapid response of the causative agent, the early investigation of the therapy to block Fas-FasL interaction and to reestablish skin integrity (Fas-receptor on the surface of cells involved in apoptosis). Massive skin damage is associated with a severe prognosis, as is the age of the baby. It is necessary to use wise the medication or automedication for a complete and effective prevention of Steven-Johnson Syndrome.*

**Keywords:** Steven-Johnson syndrome, child, tegument, medication

Steven-Johnson Syndrome (SSJ) is a rare, acute skin disorder that affects the skin and mucous membranes with severe damage to barrier function, massive water and electrolyte losses and evolution to exitus. In most cases, a direct link between the occurrence of symptomatology and the administration of a drug may be made.

SJ/NET is triggered by drugs in approximately 60-90% of children [1,2]. More than 100 drugs have been associated with this disease, including anticonvulsants, antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) being the most common triggers [3,4]. Affected patients should be exposed to the suspected drug within 8 weeks before the rash occurs, and hence the importance of the history to identify the trigger agent.

## Experimental part

### Methods and materials

One-third of patients will experience nonspecific symptoms (fever, headache, dysphagia, cough) and/or eye pruritus followed by mucosal lesions of the eyes, mouth, genitals and urinary tract in 1 to 3 days and one third of patients will experience lesions of the mucous membranes [5,6].

Clinically there are cutaneous, extracutaneous and mucosal implications.

Classical cutaneous lesions look like red-purple macules that can form large vesicles or bubbles. Traumatized areas may break out and leave deep erosion.

Eye involvement is common and may involve severe conjunctivitis and blepharitis, along with visual disturbances and photophobia. Eyes may appear swollen, erythematous and inflamed. Involvement of the respiratory tract epithelium may occur and may subsequently lead to hypoxemia, hypocapnia and acido-basal disorders [7,8].

The healing process is done by reepithelization due to the proliferation and migration of keratinocytes from the epidermis to the injured regions, often not requiring cutaneous grafts, but there is a risk of faulty healing with the appearance of sequelae. The differential diagnosis of Stevens-Johnson and NET syndrome includes multiform

erythema, viral exanthema, toxic shock syndrome, exfoliative erythroderma, and thermal burns [9,10].

Stevens-Johnson Syndrome is a well-known cutaneous reaction of type IV hypersensitivity, recognized as a disruption of cellular immunity, caused by the release of cytotoxic signals, including granulysin, perforin/granzyme B and Fas/Fas ligand that were activated by cytotoxic T lymphocytes and natural killer cells [11-13].

Anatomopathologically a massive, apoptotic keratinocyte destructive process was observed and the appearance of pathognomonic appearance of *scalding* skinned areas.

The finding of the causative agent and urgently disrupting contact with it is extremely important for survival, the risk of death being between 5 and 20%, increasing inversely in proportion to age and directly proportional to the duration of administration of the causative agent.

We live in a time of polypragmia, antipyretics, nonsteroidal antiinflammatory drugs and oral antibiotics, for example being administered without wisdom for years in children. Over the past 2-3 years, there has been a limitation on the release of antibiotics from the pharmacy, with the mandatory prescription. Obviously repercussions are extremely variable and important in case of antibiotic abuse, besides Steven-Johnson Syndrome can occur: microbial alterations, severe diarrhea, colonization with *Clostridium difficile*, development of antibiotic resistance, severe candidiasis, etc.

The specificity of the child towards the adult is an additional *wealth* of the water content, which is 65-70%. The main function of the skin, considered to be the largest organ of the body, is the barrier to microbial attacks. The other functions are not to be neglected: plastic, organ and tissue support through tactile receptors participate in the exchanges between the body and environment, intervention in the excretion function by removing toxic compounds, participation in *insipid perspiration* through mucous membranes, participation in thermoregulation, etc.

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Massive skin and mucous destructions can or cannot compensate for the functions described. Additionally, the child's immature body presents a physiological *deficiency* of its own immune system, which increases the risk of severe prognosis.

The mechanism by which a pharmaceutical compound determines potentially life-threatening side effects is not very well demonstrated. It is unanimous to accept a theory centered on an immune response to the interaction of host cells with antigens resulting from active drug metabolites, associated with a genetic predisposition consisting in a decrease in the ability of organisms to dispose of toxic compounds.

The higher the half-life of a drug, the higher the risk of Steven-Johnson Syndrome. The pathogen process involves cytokines: TNF- $\alpha$ , IL-6, IL-18, ifn- $\alpha$  and Fas ligand. In keratinocytes, there is expression of the Fas ligand-receptor ligand (CD95) Fas ligand (CD95L). Fas ligand has increased expression in Steven-Johnson syndrome and cytolytic activity, justifying the use in monoclonal antibodies in medical practice [14-16].

## Results and discussions

The clinical cases described were at 4 months interval, and affected different ages: infant (5 months) and child (3.4 years). The cases were initiated by oral antibiotic treatment, the antibiotics incriminated being Amoxicillin, respectively, Ampicillin in the young child. In infant, the clinical manifestations occurred on the 3rd day of treatment and at the child on the 6th day of treatment. It is important to note was the lack of prior antibiotherapy in the infant and the presence of polypragmazia in the case of the young child.

Clinically, the prodrome, quite specific to rhinorrhea, dysphagia, conjunctivitis, subfebrilitis, has been found in the 3.4 year old child and has been unnoticed in the baby.

The specific skin manifestations were noted in both age groups and were quite characteristic, with the evolution from the erythematous macula to the bubbles and the extensive tegumental take-off, being unequivocal in the infant, where the extension of the necrolysis process was superior to the 3 year old child. Mucosal damage was noted in both children, aggravating oral supportive treatment (Fig. 1-4).



Fig. 1.



Fig. 2.



Fig. 3.



Fig. 4.

The treatment was performed in an ATI section and was complex: antiseptic solutions, local antibiotics, nonadherent silicone dressings, daily wound dressing with the utmost attention to patient mobilization due to increased skin friability and risk of expanded skin surfaces.

The region of the face, eyes, mouth, nose, ears or anogenital was inspected daily and kept in perfect hygienic condition. In addition, parenteral nutrition, hydroelectrolytic and parenteral reequilibration, systemic corticosteroids, anti-inflammatory, high-dose intravenous immunoglobulins (for the therapeutic block of Fas-FasL interaction) were applied for 4 and 3 consecutive days, respectively.

Laboratory revealed anemia (Hb = 10.9 g/dL in the 3 year child and 10.6 g/dL in the infant), leukocytosis (L=11200 and L=14300/mm<sup>3</sup> respectively) with neutrophil left shift and neutrophilia (61 and 64% granulocytes). Transaminases were elevated in both cases, and both children had mild eosinophilia of 6 and 8%, respectively. The rest of the biological parameters were within normal limits.

Both cases had a satisfactory evolution under treatment, complete cure being achieved after about 6 weeks.

## Conclusions

Steven-Johnson syndrome, considered a rare pathological entity, is likely to occur more frequently in the child than in the adult because of the higher exposure to various inadequate therapies and due to the higher frequency of various illnesses.

In the cases presented, the tegumental detachment of 45% of the body area in the case of the infant is considered to be a process of toxic epidermal necrolysis (NET, a superior variant of Steven-Johnson syndrome, both being considered different manifestations of the same disease).

The direct relationship of skin destruction with antibiotic administration and its immediate discontinuation and the establishment of appropriate therapy increased the chances of survival.

Skin sensitization and fragility make the body susceptible to an identical reaction and in the event of possible subsequent therapies that influence long-term prognosis.

Impairment of multiple skin functions requires complex, prolonged therapy under strict conditions of asepsis and antisepsis.

Polypragmazia in recent years has created an iceberg phenomenon with regard to the affections of the Steven-Johnson and NET syndrome.

Recently, it has been found that IL-15 is useful in predicting severity and prognostic monitoring.

If IL-15 is indeed the major cytokine involved in SSJ/NET, new therapeutic modalities promise efficacy in a disease that requires a treatment option. Tofacitinib and ruxolitinib are new JAK-STAT (Janus kinase-Signal Transducer and Activator of Transcription proteins) inhibitors, inhibiting JAK 1 and 3 and JAK 1 and 2, respectively

## References

1. ROUJEAU J. Chapter 39. Erythema multiforme. In: L Goldsmith LA, Katz SI, Gilchrist BA, et al, eds. Fitzpatrick's Dermatology in General Medicine. 8th ed. New York, NY: McGraw-Hill; 2012.
2. ROUJEAU JC, KELL JP, NALDI L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med. 1995; **333**: p. 1600-1607.
3. RZANY B, MOCKENHAUPT M, BAUR S, SCHRODER W, STOCKER U, MUELLER J, et al. Epidemiology of erythema exsudativum multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis

in Germany (1990–1992): structure and results of a population-based registry. *Journal of clinical epidemiology*. 1996; **49**: p.769–773.

4. SCHOPF E, STUHMER A, RZANY B, VICTOR N, ZENTGRAF R, KAPP JF. Toxic epidermal necrolysis and Stevens-Johnson syndrome. An epidemiologic study from West Germany. *Archives of dermatology*. 1991; **127**: p.839–842.

5. MOCKENHAUPT, M. The current understanding of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Expert Rev Clin Immunol*. 2011; **7**(6):803–15.

6. MUSTAFA SS, OSTROV D, YERLY D. Severe Cutaneous Adverse Drug Reactions: Presentation, Risk Factors, and Management. *Curr Allergy Asthma Rep*. 2018;**18**(4):26.

7. SCHWARTZ RA, MCDONOUGH PH, LEE BW. Toxic epidermal necrolysis. *J Am Academy Dermatol*. 2013;**69**(2):173e1–13.

8. HENG YK, LEE HY, ROUJEAU JC. Epidermal necrolysis: 60 years of errors and advances. *British J Dermatol*. 2015;**173**(5):1250–4.

9. SASSOLAS B, HADDAD C, MOCKENHAUPT M, DUNANT A, LISS Y, BORK K, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. *Clin Pharm Ther*. 2010;**88**(1):p. 60–68.

10. FREY N, BODMER M, BIRCHER A, JICK SS, MEIER CR, SPOENDLIN J. Stevens-Johnson Syndrome and toxic epidermal necrolysis in association with commonly prescribed drugs in outpatient care other than anti-epileptic drugs and antibiotics: a population-based case-control study. *Drug Saf*. 2019 Jan;**42**(1): p. 55–66.

11. CHEN CB, ABE R, PAN RY, WANG CW, HUNG SI, TSAI YG, et al. An updated review of the molecular mechanisms in drug hypersensitivity. *J Immunol Res*. 2018;6431694.

12. CHUNG W. H., HUNG S. I., YANG J. Y., et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Nature Medicine*. 2008;**14**(12):1343–1350. doi: 10.1038/nm.1884.

13. POSADAS S. J., PADIAL A., TORRES M. J., et al. Delayed reactions to drugs show levels of perforin, granzyme B, and Fas-L to be related to disease severity. *The Journal of Allergy and Clinical Immunology*. 2002;**109**(1):155–161. doi: 10.1067/mai.2002.120563.

14. STUR K, KARLHOFFER FM, STINGL G. Soluble FAS ligand: a discriminating feature between drug-induced skin eruptions and viral exanthemas. *J Invest Dermatol* 2007; **127**: p. 802–807.

15. VIARD-LEVEUGLE I, BULLANI RR, MEDA P et al. Intracellular localization of keratinocyte Fas ligand explains lack of cytolytic activity under physiological conditions. *J Biol Chem* 2003; **278**: p. 16183–16188.

16. SU S. C., MOCKENHAUPT M., WOLKENSTEIN P., et al. Interleukin-15 is associated with severity and mortality in Stevens-Johnson syndrome/toxic epidermal necrolysis. *Journal of Investigative Dermatology*. 2017;**137**(5):1065–1073. doi: 10.1016/j.jid.2016.11.034.

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