



Relationship between Atopic Disease and Acute Ocular and Systemic Outcomes in Patients with Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

James Kwan, Harris Ahmed, Momoko K. Ponsetto, Tony Succar, James Chodosh & Hajirah N. Saeed

To cite this article: James Kwan, Harris Ahmed, Momoko K. Ponsetto, Tony Succar, James Chodosh & Hajirah N. Saeed (2022): Relationship between Atopic Disease and Acute Ocular and Systemic Outcomes in Patients with Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, Ocular Immunology and Inflammation, DOI: [10.1080/09273948.2022.2061520](https://doi.org/10.1080/09273948.2022.2061520)

To link to this article: <https://doi.org/10.1080/09273948.2022.2061520>



Published online: 29 Apr 2022.



Submit your article to this journal [↗](#)



Article views: 39



View related articles [↗](#)



View Crossmark data [↗](#)

RESEARCH ARTICLE



Relationship between Atopic Disease and Acute Ocular and Systemic Outcomes in Patients with Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

James Kwan, BSE^a, Harris Ahmed, DO, MPH^b, Momoko K. Ponsetto, BS^c, Tony Succar, PhD, MScMed(OphthSc)^a, James Chodosh, MD, MPH^a, and Hajirah N. Saeed, MD, MPH^a

^aDepartment of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Massachusetts Eye and Ear, Boston, Massachusetts, USA;

^bDepartment of Ophthalmology, Loma Linda University Medical Center, Loma Linda, California, USA; ^cSchool of Medicine, Boston University, Boston, Massachusetts, USA

ABSTRACT

Objective: To describe the relationship between history of atopic disease on systemic and ocular manifestations of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN).

Methods: Retrospective chart review of patients with SJS/TEN patients. Those with and without prior atopic diagnosis were compared.

Results: In total, 200 patients with SJS/TEN were identified. A total of 23 patients also had an atopic diagnosis. Four, 10, and 18 had atopic dermatitis, allergic rhinitis, and asthma respectively. Acute ocular severity was significantly worse in the atopic cohort. No significant differences in overall systemic severity of SJS or mortality were found between the atopic and non-atopic cohorts. Compared to our hospital system's general population, prevalence of an atopic diagnosis was significantly higher in those with SJS/TEN.

Conclusion: Patients with a history of an atopic diagnosis appear to have more significant acute ocular involvement during their SJS/TEN hospitalization. Atopic conditions appear to occur more frequently in the SJS/TEN population compared to the general population.

ARTICLE HISTORY

Received 16 August 2021

Revised 15 March 2022

Accepted 29 March 2022

KEYWORDS

Allergic rhinitis; asthma; atopic dermatitis; atopic triad; atopy; Stevens-Johnson syndrome; toxic epidermal necrolysis

Introduction

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) are severe cutaneous hypersensitivity reactions typically incited by medications or infections. These disease entities exist on a spectrum and are characterized by the blistering and sloughing of the skin and mucous membranes.¹ SJS is the milder form with less than 10% of total body surface area involvement, and TEN is the more severe form with over 30% total body surface area involvement. SJS/TEN is characterized by acute blisters arising on macules on the skin and at least two sites of mucous membrane involvement such as the ocular surface, oral cavity, and genitals. Symptoms of SJS/TEN include high fever, erythema, erosion, blisters occurring over the entire body, particularly the eyes, mouth, vulva and oral cavity¹⁻⁶ which can ultimately lead to death due to concomitant severe complications such as sepsis, respiratory insufficiency, and multiple organ failure.⁶

The precise pathomechanism of SJS/TEN is unknown. controversial and efforts are currently underway to elucidate this process. The involvement of immune mechanisms, altered drug metabolism, and bacterial and viral infections such as *Mycoplasma pneumoniae* and herpes viruses have all been suggested.⁷ SJS/TEN is considered a type IVc delayed hypersensitivity reaction which is mediated by T cells.

Type I hypersensitivity reactions, on the other hand, involve B-cell-mediated IgE release in response to re-exposure to an allergen. Subsequent exposures cause sensitized mast cells to

degranulate, resulting in the release of factors including histamine, leukotrienes, prostaglandins, and cytokines. Atopy is a predisposition to respond immunologically to diverse antigens/allergens, and is a Type I hypersensitivity reaction. The clinical consequence of this is the propensity to develop hypersensitivity reactions to allergens (InSTAT). A history of atopy has been shown to be associated with more severe disease courses in COPD, juvenile systemic lupus erythematosus, juvenile idiopathic arthritis, and others.⁸⁻¹⁰ There is also increasing evidence for the association of atopic conditions with certain cancers, cardiovascular diseases, infections and neuropsychiatric disorders. Atopic diseases have also been associated with several autoimmune conditions, including dermatologic diseases such as dermatitis herpetiformis, alopecia areata, pemphigoid/pemphigus, and psoriasis. No associations between atopic disease and SJS/TEN have been reported and it is unknown whether type I hypersensitivity reactions such as those in atopic conditions are associated with an increased risk of type IV HSN reactions like SJS/TEN. There are also no studies evaluating acute ocular disease in these cohorts of SJS/TEN patients.⁹ The atopic triad, consisting of allergic rhinitis, asthma, and atopic dermatitis, are classic and common examples of type I hypersensitivity reactions. In this study we sought to assess the relationship between a history of atopic disease and the development of SJS/TEN as well as related ocular disease. To our knowledge, this is the first study of its kind to investigate this relationship.

METHODS

Subjects and Study Design

We retrospectively identified patients hospitalized at all Mass General Brigham hospitals between 1979 and December 2020 with a diagnosis of SJS, SJS-TEN overlap, or TEN. Medical records were obtained from all Mass General Brigham hospitals with electronic medical records available on Epic.

Patients with a history of SJS, SJS-TEN overlap, or TEN, and asthma, atopic dermatitis, or allergic rhinitis were identified using the Research Patient Data Registry (RPDR) tool. All patients at Mass General Brigham with a history of asthma, atopic dermatitis, and allergic rhinitis were also identified to establish a baseline frequency of these diagnoses. Diagnosis of SJS/TEN was confirmed with clinical confirmation by the dermatology or burn service including evaluation of skin biopsy. Diagnosis of asthma, atopic dermatitis, and allergic rhinitis were clinically confirmed with chart review indicating history of each respectively per guidelines from the American Academy of Family Physicians, U.K. Working Party's Diagnostic Criteria, and the American Academy of Otolaryngology-Head and Neck Surgery, respectively.^{11–13} Once diagnoses were confirmed, cohorts included SJS/TEN and: asthma; atopic dermatitis; or allergic rhinitis. Eighteen, four, and ten patients were identified respectively. Comparative prevalence of the presence of atopic conditions in the SJS/TEN population against the general MGB population was calculated.

Acute Ocular Severity Scores

The acute phase of disease was defined as the interval between onset of initial skin lesions and 1 month after their development. We have previously described acute ocular grading and treatment.¹⁴ Scores ranged from 0 to 3, depending on the presence of conjunctival, corneal, and eyelid margin disease. The worst acute ocular severity score during the acute phase of the initial SJS/TEN admission was the primary ocular outcome of interest.

Statistical Analysis

All data analyses were performed using R 4.0.2 (R Core Team, 2020). The means and standard deviations are presented for ordinal variables. Odds ratios are presented as proportions. Kruskal–Wallis tests were performed to assess the relationship of coexisting asthma, atopic dermatitis, and allergic rhinitis on the severity of the acute ocular severity scores. Statistical significance was defined as $p < .05$.

RESULTS

Patient Characteristics

Patient demographics and characteristics of systemic disease are summarized in Table 1. The mean age at the time of SJS/TEN diagnosis within the atopic cohort was

Table 1. Demographic data for atopic vs. nonatopic SJS/TEN patients.

	Atopy in SJS/TEN	Non-atopic SJS/TEN Controls	p
n	23	177*	–
Age	38.1 ± 22.7	47.9 ± 22.6	0.0751 [†]
Male (n)	9	71	0.6553 [†]
Ethnicity			
Hispanic	1	12	1
Non-Hispanic	22	148	0.2213
Unknown	0	17	0.2280
Spectrum			
SJS	9	76	0.503 [†]
SJS-TEN Overlap	4	25	1 [†]
TEN	10	54	0.4868 [†]

[†]Kruskal–Wallis test; [†]Fisher's Exact test

SJS/TEN = Stevens Johnson syndrome/toxic epidermal necrolysis

Table 2. Inciting agents for SJS/TEN in atopic vs nonatopic SJS/TEN patients.

	Atopy in SJS/TEN	Non-atopic SJS/TEN Controls	p
n	19	128	–
Antibiotics	7	49	1
Bactrim	4	32	1
Penicillins/Beta-Lactams	1	4	0.5046
Macrolide	0	4	1
Cephalosporins	1	4	0.5046
Fluoroquinolone	0	3	1
Vancomycin	1	1	0.2426
Tetracycline	0	0	1
Clindamycin	0	1	1
Age, years	41.71	49.86	0.3948
Analgesics	3	18	0.7366
Acetaminophen	0	4	1
NSAIDs	3	14	0.4628
Age, years	21.54	31.53	0.3149
Antiepileptics	3	24	1
Lamotrigine	3	17	0.7248
Phenytoin	0	2	1
Carbamazepine	0	5	1
Age, years	26.36	41.33	0.4875
Allopurinol	0	7	0.5952
Unknown	1	9	1

Note smaller sample size as only patients with one reported most likely etiology were included in this analysis

SJS/TEN = Stevens Johnson syndrome/toxic epidermal necrolysis

numerically lower at 38.1 ± 22.7 compared to 47.9 ± 22.6 in the non-atopic control group however this difference was not found to be significant ($p = .0751$). Additionally, sex and frequency of presentation with SJS, SJS-TEN Overlap, or TEN was not found to be significantly different between groups.

Causative agents were not found to be more significantly clustered in the atopic cohort versus control. Patients were included only if one or no known causative agent was implicated in the development of SJS/TEN. Nineteen atopic patients and 128 control patients of the original cohorts were included for this analysis. Furthermore, when agents were grouped into larger categories including antibiotics, analgesics, and antiepileptics, no significant differences in the frequency of inciting SJS/TEN or age at time of diagnosis were noted. These findings are summarized in Table 2.

Table 3. Acute ocular severity and mortality is atopic vs non-atopic SJS/TEN patients.

	Atopic SJS/TEN Patients N = 23	Non-atopic SJS/TEN Controls N = 177	p
Acute Ocular Severity Score	1.652 ± 1.265	1.000 ± 1.032*	0.0154-††
Acute Mortality	1/23 (5.35%)	31/177 (17.51%)	0.1352

SJS/TEN = Stevens Johnson syndrome/toxic epidermal necrolysis

*155 patients were included in the control AOS score calculation due to availability of AOS scores

Acute Ocular Outcomes

Summarized results of acute ocular outcomes are found in Table 3. Twenty-three unique patients with atopic conditions and confirmed history of SJS/TEN were included from the initial RPDR population search. Of these patients with SJS/TEN, four had prior history of atopic dermatitis, ten had allergic rhinitis, and eighteen had asthma. The total number of patients overall reflects a smaller number than the sum of the three subgroups as several patients had history of a combination of the atopic conditions. One hundred seventy-seven SJS/TEN patients without history of any of the atopic conditions were additionally included to serve as a control group, of which 155 had AOS scores available for comparative analysis of ocular outcomes.

The cohort of unique patients with any atopic condition had a significantly higher mean AOS score of 1.652 as compared to 1.000 ($p = .0154$, Table 2). All patients had undergone treatment including amniotic membrane transplantation based on a previously described protocol.¹⁵ Patients who did not receive protocol treatment were not included in analysis.

Acute Mortality

The number of patients and corresponding rates of acute mortality in atopic versus nonatopic SJS/TEN patients during the initial hospitalization for SJS/TEN are summarized in Table 3. One patient out of 23 from the atopic cohort and 31 patients out of 177 from the control cohort died acutely. Though acute mortality was found to be lower in the atopic cohort, this finding was not statistically significant.

Relative Prevalence of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis according to Atopic Triad Constituent

The comparative prevalence of atopic dermatitis, allergic rhinitis, and asthma between the SJS/TEN population and the general MGB population are shown in Table 4. The rates of atopic conditions occurred at significantly higher rate within our SJS/TEN population compared to the MGB population overall. Incidence rates could not be calculated in this non-longitudinal study.

Table 4. Relative prevalence of atopy in the SJS/TEN population versus the general patient population within MGB; ^{††} statistically significant at $\alpha < 0.05$.

	General MGB Population, n	SJS/TEN at MGB, n	Prevalence Ratio	p
Atopy (atopic dermatitis, allergic rhinitis, or asthma), n	6,452,461 131,874	200 23	– 5.75	– <0.0001 ^{††}

MBG = Mass General Brigham; SJS/TEN = Stevens Johnson syndrome/toxic epidermal necrolysis

DISCUSSION

SJS/TEN is considered a type IVc hypersensitivity reaction.¹⁶ It is most commonly caused by the introduction of an inciting medication but may develop idiopathically, by inflammatory conditions, or infection.^{16–22} Type I hypersensitivity reactions such as atopic diseases are associated with other autoimmune diseases but such a relationship has not been described in the setting of SJS/TEN. The effect of atopic disease on the severity of ocular disease has also not been described. We have found a significantly increased prevalence of history of atopic disease among patients with SJS/TEN compared to our controls. Peak acute ocular severity in patients with SJS/TEN was also worse in those with a history of atopic disease.

The literature is mixed on the detrimental versus protective effect of atopy on various conditions. Linos et al. reported on the relationship between atopic dermatitis and the development of gliomas and reported a lower incidence of tumor development in those with a history of atopic dermatitis.^{23,24} They postulated this may be due to the hyperactive immune system mitigating the proliferation of cancerous cells. A review of the literature by Wang et al. corroborated this finding by describing the apparent protective role of atopy on the development of various types of cancer, ranging from brain to colorectal.²⁵

However, atopy may be a risk factor for disease severity and extrapulmonary manifestations in children with mycoplasma pneumonia which is on the spectrum of SJS/TEN disease when associated with mucositis.²⁶ IgE-mediated mechanisms have been implicated in multiple diseases with an autoimmune component. For example, pemphigus vulgaris, an autoimmune bullous skin disease, is known to primarily be caused by auto-IgG against desmoglein 3; however, it was noted by Nagel et al. that patients with elevated IgE levels were observed to have more exaggerated acute onset of disease when compared against those with lower levels.²⁷ We do not have IgE data on our patients but a history of atopy might serve as a proxy for elevated IgE. The literature on atopy, IgE, and SJS/TEN is sparse. One case report describes a case of TEN due to ceftriaxone and subsequent acute IgE mediated skin hypersensitivity to an extended spectrum penicillin. The patient had a history of atopic skin disease and rhinitis preceding his hospitalization for TEN. The authors commented that though the history of atopy by itself does not seem to be an independent risk factor for antibiotic allergy, it may predispose patients to more severe and even fatal reactions in the event of anaphylaxis. IgE levels during the TEN episode were not mentioned.²⁸ Another case report described successfully treating a patient

with TEN secondary to levofloxacin with pulse prednisolone and an anti-IgE monoclonal antibody, omalizumab. Pulsed steroid has been shown to provide an ocular and mortality benefit in SJS/TEN and it is unclear how, if at all, the effects of the steroid versus omalizumab were differentiated.^{29,30} There are no studies on the levels of IgE in SJS/TEN in the literature and future studies are needed to establish a relationship between IgE levels and severity of systemic and ocular disease in SJS/TEN.

The atopic triad was chosen as a proxy to represent type I hypersensitivity as each of its components (atopic dermatitis, allergic rhinitis, and asthma) have an established IgE-mediated component in their pathogenesis.⁸ Our hypothesis was that patients with a history of any atopic condition would be at higher risk for subsequent development of SJS/TEN and may go on to develop more severe acute disease manifestations. Our data demonstrated a significantly higher prevalence of atopy within the SJS/TEN population compared to the general MGB population. We compared prevalence within the MGB system rather than against national statistics as patients within the MGB system are likely uniquely different than those of the general population. The significance of higher prevalence of atopy within the SJS/TEN cohort is unclear and the interplay between types I and IV hypersensitivities has not been extensively studied. The pathogenesis for atopic triad is well-described involving Th2 cell-mediated inflammation and subsequent secretion of cytokines. There may be an overlap between the cytokine profiles of atopic disease and SJS that may explain the link between the two diseases seen here in our study. IL-8 and IP-10 are cytokines that have been found to be elevated in the tears of patients of SJS and also in skin lesions of patients with atopic dermatitis and psoriasis. Other interleukins, such as IL-13 have been found to be elevated in skin lesions of both atopic dermatitis and SJS/TEN patients, but not in tears.^{6,31,3231,31,3232} In our study, while ocular severity was correlated with history of atopy, severity of systemic disease and mortality were not. It may be that the differential expression of cytokine profiles on the ocular surface vs systemically plays a role in the severity of ocular disease in those with a history of atopy.

Acute ocular involvement was noted to be significantly worse at its peak in the atopic population compared to non-atopic controls. While chronic ocular disease was not investigated in this study, we have previously shown that worse acute ocular disease in SJS/TEN leads to worse chronic outcomes.¹⁴ While established protocols have shown success in mitigating the severity of disease in SJS/TEN in general, we are unsure of how a history of atopic disease should affect acute-stage treatment. Further studies on this cohort alone are needed to modify current accepted treatment practices in addition to clarifying the role of IgE mediated disease in exacerbating SJS/TEN severity and outcomes.

There are several limitations to this study. First is the inherently small sample size given the rarity of this disease. While AOS was found to be significantly different between atopic and non-atopic SJS/TEN patients, the nonsignificant results for other variables may be due to low sample size or may truly reflect no differences between groups. Certain variables, such as acute mortality had clinically significant group differences but

were not statistically significant. Larger multi-center studies may further elucidate this relationship. Secondly, the patient population at MGB is likely unique compared to that of the general population and it is unknown how that affects our outcomes and how applicable they are to other populations. However, even between the SJS/TEN subset of patients with atopic disease versus no atopic disease, who followed the same treatment protocol, acute disease was significantly different between the two groups. Our study also does not quantitatively assess active atopic disease in the form of IgE measurement or history of most recent episode, and relies on history as documented in the medical record. Still, this is the first study to investigate the possible role of atopic disease in SJS/TEN.

A history of atopic disease in the form of components of the atopic triad appear to be more common in patients with SJS/TEN than those of the general hospital population. While SJS/TEN and atopic disease are different types of hypersensitivity reactions, the development of one may influence the other. More severe ocular disease is also seen in SJS/TEN patients with a history of atopic disease but further study is needed to understand how this impacts acute treatment. Next steps include investigating the effect of the presence of atopy on the timing of peak systemic and ocular symptoms as well as serial measurements of serum IgE and other immune mediators.^{31,32}

Acknowledgments

The project described was supported by the National Eye Institute, National Institutes of Health, Award Number K23EY028230. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Disclosure Statement

No potential conflict of interest was reported by the author(s).

Funding

This work was also conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL1TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers. Funding was also received by NIH/NEI Award K23EY028230.

References

1. Kohanim S, Palioura S, Saeed HN, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis – a comprehensive review and guide to therapy. I. Systemic disease. *The Ocular Surface*. 2016 Jan;14(1):2–19. doi:10.1016/j.jtos.2015.10.002. Epub 2015 Nov 5. PMID: 26549248.
2. Power WJ, Ghoraihi M, Merayo-Llves J, Neves RA, Foster CS. Analysis of the acute ophthalmic manifestations of the erythema multi-forme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease spectrum. *Ophthalmology*. 1995;102(11):1669–1676. doi:10.1016/S0161-6420(95)30811-1.
3. Howard GM. The Stevens-Johnson syndrome: ocular prognosis and treatment. *Am J Ophthalmol*. 1963;55(5):893–900. doi:10.1016/0002-9394(63)90366-0.
4. Lehman SS. Long-term ocular complication of Stevens-Johnson syndrome. *Clin. Pediatr. (Phil.)*. 1999;38(7):425–427. doi:10.1177/00092289903800709.

5. Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch. Dermatol.* 1993;129(1):92–96. doi:10.1001/archderm.1993.01680220104023.
6. Yoshikawa Y, Ueta M, Nishigaki H, et al. Predictive biomarkers for the progression of ocular complications in chronic Stevens-Johnson syndrome and toxic Epidermal necrolysis. *Sci Rep.* 2020;10(1):18922. doi:10.1038/s41598-020-76064-8.
7. Harr T, French LE. Toxic epidermal necrolysis and Stevens–Johnson syndrome. *Orphanet J Rare Dis.* 2010;5(1):39. doi:10.1186/1750-1172-5-39.
8. Abbas M, Moussa M, Akel H Type I hypersensitivity reaction. [Updated 2020 Oct 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021
9. Guo R, Cao L, Kong X, Xue H, Li X, Shen L. Atopy in children with the enthesitis-related arthritis (ERA) subtype of juvenile idiopathic arthritis is associated with a worse outcome. *Eur J Pediatr.* 2015 Nov;174(11):1441–1450. doi:10.1007/s00431-015-2553-1. Epub 2015 May 3. PMID: 25935591.
10. Ivert LU, Wahlgren CF, Lindelöf B, Dal H, Bradley M, Johansson EK. Association between atopic dermatitis and autoimmune diseases: a population-based case-control study. *Br J Dermatol.* 2020 Oct 22;185(2):335–342. doi:10.1111/bjd.19624. Epub ahead of print. PMID: 33091150.
11. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's diagnostic criteria for atopic dermatitis. III. Independent hospital validation. *Br J Dermatol.* 1994 Sep;131(3):406–416. doi:10.1111/j.1365-2133.1994.tb08532.x.
12. <https://www.entnet.org/quality-practice/quality-products/clinical-practice-guidelines/allergic-rhinitis>. Accessed July.18,2021.
13. Asthma: updated diagnosis and management recommendations from GINA – practice guidelines. *Am Fam Physician.* 2020 Jun 15;101(12):762–763.
14. Shanbhag SS, Rashad R, Chodosh J, Saeed HN. Long-term effect of a treatment protocol for acute ocular involvement in Stevens-Johnson syndrome/toxic epidermal necrolysis. *Am J Ophthalmol.* 2019 Dec;208:331–341. doi:10.1016/j.ajo.2019.07.006. Epub 2019 Jul 19. PMID: 31326519; PMCID: PMC7935472.
15. Bellón T. Mechanisms of severe cutaneous adverse reactions: recent advances. *Drug Saf.* 2019 Aug;42(8):973–992. doi:10.1007/s40264-019-00825-2. PMID: 31020549.
16. Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol.* 1990;126(1):43–47. doi:10.1001/archderm.1990.01670250049006.
17. Cooney R, Beck A, Gonzalez B, Gamelli RL, Mosier MJ. Not all drugs are created equal: the importance of causative agent in toxic epidermal necrolysis. *J Burn Care Res.* 2016;37(1):e69–78. doi:10.1097/BCR.0000000000000328.
18. Mockenhaupt M, Kelly JP, Kaufman D, Stern RS, Group SS. The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with nonsteroidal antiinflammatory drugs: a multinational perspective. *J Rheumatol.* 2003;30:2234–2240.
19. Mockenhaupt M, Viboud C, Dunant A, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol.* 2008;128(1):35–44. doi:10.1038/sj.jid.5701033.
20. Parrillo SJ. Stevens-Johnson syndrome and toxic epidermal necrolysis. *Curr Allergy Asthma Rep.* 2007;7(4):243–247. doi:10.1007/s11882-007-0036-9.
21. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med.* 1995;333(24):1600–1607. doi:10.1056/NEJM199512143332404.
22. Sharma VK, Sethuraman G, Minz A. Stevens Johnson syndrome, toxic epidermal necrolysis and SJS-TEN overlap: a retrospective study of causative drugs and clinical outcome. *Indian J Dermatol Venereol Leprol.* 2008;74(3):238–240. doi:10.4103/0378-6323.41369.
23. Disney-Hogg L, Cornish AJ, Sud A, et al. Impact of atopy on risk of glioma: a Mendelian randomisation study. *BMC Med.* 2018 Mar 15;16(1):42. doi:10.1186/s12916-018-1027-5. PMID: 29540232; PMCID: PMC5853158.
24. Linos E, Raine T, Alonso A, Michaud D. Atopy and risk of brain tumors: a meta-analysis. *J Natl Cancer Inst.* 2007;99(20):1544–1550. doi:10.1093/jnci/djm170.
25. Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. *Allergy.* 2005 Sep;60(9):1098–1111. doi:10.1111/j.1398-9995.2005.00813.x. PMID: 16076292.
26. Wang Z, Sun J, Liu Y, Wang Y. Impact of atopy on the severity and extrapulmonary manifestations of childhood Mycoplasma pneumoniae pneumonia. *J Clin Lab Anal.* 2019;33(5):e22887. doi:10.1002/jcla.22887.
27. Nagel A, Lang A, Engel D, et al. Clinical activity of pemphigus vulgaris relates to IgE autoantibodies against desmoglein 3. *Clin Immunol.* 2010 Mar;134(3):320–330. doi:10.1016/j.clim.2009.11.006. Epub 2009 Dec 16. PMID: 20015693.
28. Lam A, Randhawa I, Klausermeyer W. Cephalosporin induced toxic epidermal necrolysis and subsequent penicillin drug exanthem. *Allergol Int.* 2008 Sep;57(3):281–284. doi:10.2332/allergolint.C-07-55. Epub 2008 Jul 1. PMID: 18566552.
29. Araki Y, Sotozono C, Inatomi T, et al. Successful treatment of Stevens-Johnson syndrome with steroid pulse therapy at disease onset. *Am J Ophthalmol.* 2009 Jun;147(6):1004–1011. 1011. 1. doi: 10.1016/j.ajo.2008.12.040. Epub 2009 Mar 14. PMID: 19285657
30. Tripathi A, Ditto AM, Grammer LC, et al. Corticosteroid therapy in an additional 13 cases of Stevens-Johnson syndrome: a total series of 67 cases. *Allergy Asthma Proc.* 2000 Mar-Apr;21(2):101–105. doi:10.2500/108854100778250914. PMID: 10791111.
31. Giustizieri ML, Mascia F, Frezzolini A, et al. Keratinocytes from patients with atopic dermatitis and psoriasis show a distinct chemokine production profile in response to T cell-derived cytokines. *J Allergy Clin Immunol.* 2001 May;107(5):871–877. doi:10.1067/mai.2001.114707. PMID: 11344355.
32. Sadek M, Iqbal O, Siddiqui F, et al. The role of IL-13, IL-15 and granulysin in the pathogenesis of Stevens-Johnson syndrome/toxic epidermal necrolysis. *Clin Appl Thromb Hemost.* 2021 Jan-Dec; 27:1076029620950831. doi:10.1177/1076029620950831. PMID: 33560872; PMCID: PMC7876748.