Efficacy and tolerance of ALLERGIKA®- Eyelid cream.

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ABSTRACT
Periorbital dermatitis is a frequent problem in dermatological practice. Patients diagnosed with this disease not only report subjective complications but also psychological problems as the disease is in a visible location. Because of the variety of causes of clinical findings, differential diagnostic is rather challenging. Following most of the international guidelines, the drug of first choice is generally a topical corticosteroid with lower intensity of therapeutic effect. However, frequent and long-term treatment with local topical corticosteroids has multiple adverse effects. Once the acute stage is successfully managed, the treatment should be substituted by soothing emollients to improve and restore skin barrier function.

AIM: The aim of this study was to evaluate efficacy and tolerance of lipophilic ALLERGIKA® - eyelid cream containing quadruple active ingredient complex of 10% glycerol, Allantoin, Bisabolol and Vitamin E with clinically proven efficacy on inflammatory manifestations in skin as well as hydratating and skin barrier protection effect described in the literature.

MATERIAL AND METHODOLOGY: The study was carried out at the Clinic of Dermatovenerology at the University Hospital in Bratislava, Faculty of Medicine, Comenius University in Bratislava and dermatological out-patient department BELLAMED s.r.o. in Brezno. 26 patients were enrolled into the study, of that 4 withdrew during the study period. The study collected data from 22 patients, of that 4 (18%) men and 18 (82%) women. The study assessed erythema, dryness and scaling in the regions of upper and lower eyelids. After taking patient's medical history and clinical examination, the subjects were prescribed local treatment with ALLERGIKA®-Eyelid cream for a period of three weeks, when the patients were thoroughly monitored. The state of a disease was scored according to the Investigator Global Assessment (IGA) system (assessment by a medical doctor) and Patient Global Assessment (PGA) (patient's assessment) and based on clinical findings and photo documentation.

RESULTS: Total score from both scoring systems IGA and PGA throughout the study period demonstrated a remarkable decrease in values which suggests improvement of patient's condition. Based on the photographic documentation and results from the scoring systems we assessed significant resolution of clinical symptoms in most of the patients.

CONCLUSION: Topical lipophilic emollient seems to be efficacious and helpful in treatment of periorbital dermatitis manifested by erythema, skin dryness and desquamation. At the same time, it is suitable for a long-term, prophylactic treatment.

KEY WORDS: eyelid, periorbital dermatitis, emollients

INTRODUCTION
Periorbital dermatitis is a frequent challenge in dermatology. It is significantly represented in differential diagnostics, often practiced also by ophthalmologists. The condition is frequent, yet often difficult to cure. Patients diagnosed with periorbital dermatitis often suffer severely as the disease is at visible location. Due to diversity causes of the clinical findings, diagnostics is challenging. (5).
The core of the examination and diagnostics is to take medical history which is, almost a detective type of work, aimed at identifying causes and physical examination. Possible causes include allergic contact dermatitis, irritation contact dermatitis, atopic dermatitis, seborrheic dermatitis, psoriasis, infections, rosacea and others. Dermatitis of eyelids can result from a combination of various factors, e.g. allergic contact dermatitis, secondarily manifested at a different unhealthy background, such as atopic dermatitis or seborrheic dermatitis. It can also manifest itself as an iatrogenic complication of treatment of another disease. (1,5).
Generally, most world guidelines recommend topical local corticosteroid with lower intensity of therapeutic efficacy as a drug of first choice. The disease tends to be persistent and frequent, long-term treatment has many adverse effects (skin atrophy, teleangiectasia, rebound phenomenon). Therefore, it should be, in later stages, replaced by soothing emollients that also improve and restore the skin barrier function(9).

The skin around eyes is very thin (0.55 mm in comparison with other facial areas with standard thickness of skin around 2.0 mm). Therefore, it allows locally applied substances, but also airborne allergens, easily penetrate through it. Thus, even if an allergen gets into contact with other areas of the body, the reaction can manifest itself on the eyelids (4).

Etiology
Dermatitis can be, depending on its origin, divided into two main groups – dermatitis of exogenous origin (irritant contact dermatitis (ICD), allergic contact dermatitis (AC), microbial dermatitis and others) and that of endogenous origin (atopic

dermatitis, seborrheic dermatitis, psoriasis and others). It is also important to assess if a patient is in acute or chronic stage. Acute stage is characteristic with its polymorphy, such as erythema, edema, papules, vesicular manifestations, weeping, scrabs. Chronic phase can manifest itself with lichenification, desquamation, hyperostosis (1).

The causes of dermatitis may be multiple. The first potential cause may be cosmetics. Beauty cosmetics contains pigments, often with paraphenylediamines (PPD), nickel and oxides of iron. Also, there are different ingredients that are irritants and allergens. Eyelash mascaras and eye shadows contain rosins, colophony, solvents. Glossy powders contain aluminium, oxides of bismuth and titanium. Further ingredients include preservatives, such as paraben esters, sodium sorbate, benzalkonium chloride and others (7).
Ingredients and additives in eye and face creams may cause irritant or allergic symptoms in periorbital area. Hair and nail preparations may also lead to skin manifestations in this area, usually in the form of delayed allergic reactions. Forms of early reactions may vary, including extra cutanneous, e.g. respiratory reactions.
Well known allergens in ophthalmology include phenylephrine, beta blockers, antibiotics, resorcinol, pilocarpine, thiomersal, chloramphenicol and antazoline (6,7).

Irritant contact dermatitis (ICD)
It is a localized inflammatory reaction of skin based on a direct cytotoxic effect of irritants. It establishes itself through a primary single exposure to irritant exogenous agents.

Acute ICD is caused by exposure to a strong irritant effect. Typical symptoms include erythema, edema, vesicula or bullae, almost erosions, exsudation and necrosis, with an onset shortly after the exposure to the irritant. Typical subjective symptoms include burning, itchy rash, pruritus and pain in the skin. Lesions show sharply defined borders, limited to the contact area since the concentration of the substance, when pervading into the surrounding area drops below the threshold value that induces reaction.
Diagnostics of an acute ICD is usually easy since the skin lesions appear suddenly after exposure, which points to the causal factor. Usually, the onset is very fast. (4).

There is also clinical experience with delayed acute ICD. The onset of symptoms may be delayed by 8 to 24+ hours. Clinical manifestations and the development of a condition are very similar to that of acute ICD. Delayed onset can be misdiagnosed as allergic contact dermatitis (ACD). Therefore, it is advised to take thorough medical history and epicutaneous tests that lead to precise diagnosis (5).

Chronic or cumulative forms of ICD result from a repeated exposure to various irritants with lower irritant potential unable to provoke an acute ICD in a given concentration. The eyes are often exposed to volatile irritants or cosmetics. Clinically, chronic ICD manifestations include erythema, scaling, lichenification, hyperkeratosis and skin fissures (5).

Airborne contact dermatitis includes various types of dermatitis (e.g. acute, chronic and subjective dermatitis). It is caused by substances released into the air that settle down on skin. Many airborne agents can be found in working environment, present in different forms, e.g. as fibres, dust particles, sprays, mist, evaporations and gases. Eyelids are especially sensitive to those agents due to higher level of penetration through their thin skin. (4,5).

Allergic contact dermatitis (ACD)
ACD is a typical manifestation of a delayed sensitive reaction type IV. to exogenous agent. Clinically, it occurs after the exposure to the allergen after the prior sensibilization of a person. It can also manifest itself after many years of exposure to the allergens (10).
The acute stage is characteristic by erythema, induration and scaly patches of skin. Severe cases can also manifest themselves as vesicular and bullous lesions in affected areas. Eyelid manifestations may include severe puffiness combined with severe itching. Repeated or systematic exposure of a sensibilized individual to the allergen may lead to chronic condition, often presented as erythematic lichenificated focuses with hyperkeratosis, scaly patches and skin fissures.
There are more than 3,700 allergens causing ACD in humans. The most prevalent allergens affecting eyelids include preservatives (used in cosmetics, topical medications and contact lens care solutions), aromatic substances and rosin used in nail polish. Therefore, a transfer of antigen from hands to eyelids should be considered (1,4).

Atopic dermatitis
Atopic dermatitis is a chronic, relapsing, itching inflammatory skin condition. It is usually combined with higher levels of IgE in the serum, personal and family history of atopic condition present in a cluster of diseases, including atopic dermatitis, asthma and allergic rhinitis (12).
The pathogenesy of atopic dermatitis combines various factors, including abnormality of skin barrier, congenital and acquired (Th2) immunodeficiency disorders, and changed microbial flora of the skin.
When it comes to patients with atopic dermatitis, frequent characteristic in periorbital area is double Dennie-Margan fold even at calm skin.

Main symptoms of atopic dermatitis are dominated by dryness of skin and massive pruritus. Eyes may tear excessively, producing white eye discharge. During exacerbation stage, the symptoms tend to worsen very fast. Itching is replaced by extremely unpleasant feeling of pain and that of external object and subsequent deterioration of vision. It may be more difficult to open eyelids in the morning due to a combination of discomfort and secretion. Other frequent symptoms include erythema, mild edema and lichenification.
Clinical symptoms in patients with AD may get complicated by microbial superinfection and sensibilization (13,14).

Table 1 Framework differential diagnostic characteristics of eczema and dermatitis

UNIT	MORPHOLOGY	LOCATION	SYMPTOMS	DEVELOPMENT
Irritant contact dermatitis	Monomorphic appearance, sharply demarcated erythema, edema. Skin is dry, rough. Chronic ICD – hyperkeratosis, desquamation, lichenification and skin fissures.	Maximum at the place of contact but there can also be a generalized dermatitis	Burning, itching, pain and skin pain (with possible pruritus)	Acute phase manifests abruptly, after the first exposure (to a strong irritant). Lesions manifest themselves rapidly, several minutes after exposure but there may also be delayed reactions. Typical *decrescendo* phenomenon – reaction quickly peaks after an exposure and then starts to heal. Relapse only in contact with the same substance.
Allergic contact dermatitis	Polymorphic appearance, papulovesicular, edema, weeping skin. (Pustules and necrosis are rare). Poor delineation.	Erythema poorly delineated, maximum in the place of contact, dispersed into surrounding area.	Pruritus as main symptom.	Sensibilization needed. Lesions usually appear 24-72 hours after the exposure but can already develop after 5 hours or later; seven days after the exposure. Characteristic *crescendo* phenomenon. – Relapse when skin barrier neglected.
Atopic dermatitis	Polymorphic appearance, papule-vesicula, lichenification.	Predilection of flexure areas at extremities, stigmatisation	Skin dryness, significant pruritus, double Dennie-Morgan fold	Chronic, relapsing

Therapy:
Multistage therapy is recommended. First step is to take medical history, identify trigger and eliminate it. Next therapeutic step is to treat inflammatory manifestations at the skin and restore skin barrier. It is important to protect skin against a relapse, inform a patient about potential alternatives and secure more detailed level of information on the products' ingredients (1,4,9).

Even if the first therapeutic step is to eliminate trigger, in most cases, treatment to remedy inflammatory manifestations around eyes is needed. The core therapeutic approach is to apply local treatment that is active directly on the affected area. This is both safe and advantageous since the body is not burdened as in the case of systemic treatment. One needs to be beware of individual reactivity of skin and different tolerance to medical product. The efficacy also depends on regularity of treatment (1).
The first line are local topical corticosteroids. Recommendation is to apply those with low or mid-low intensity of therapeutic efficacy (from 6 grade scale of corticosteroids). Local tacrolimus (0.1%) or pimecrolimus (1% cream applied 2 a day) is used as the first alternative. Generalized cases are suitable for a systemic treatment with corticosteroids mainly when local steroids are not effective or fast relieve in the area of affected eyelids is needed. Imunomodulatory medications as azathioprine, mycophenolate mofetil, cyclosporine are used rarely, only with chronic dermatitis (1,4,9).

The most frequent treatment with highest efficacy is application of local corticosteroids used in clinical practice for their antiinflamatory characteristics and quick onset of effect. However, local corticosteroids should not be applied as a long term treatment due to their numerous adverse effects.

Emollients and hydratating preparations are beneficial in all patients with periorbital dermatitis. They soften stratum corneum, lower transepidermal loss of water and attract water into stratum corneum. They are used to lower irritation, improve and restore function of skin barrier. They are efficacious only when on skin, therefore they should be applied several times a day.
Occlusive emollients (e.g. vaseline, lanoline, mineral oils, vegetal oils, beewax, ceramides and silicones) slower transepidermal loss of water, hydratants (e.g. glycerine, sorbitol, propylenglycol or topic urea) are hygroscopic substances with high ability to attract water into stratum corneum and deeper epidermis and dermis (5,9,11,12).

Methodology
The condition of the disease was assessed by a medical doctor - dermatologist (IGA) and patient (PGA) at all three visits. Assessed values included: the degree of erythema (on score from 0 to 3, while 0 = without manifestations of erythema; 3 = serious erythema), dryness of skin (0 = no manifestations of dryness to 3 = serious dryness of skin), scaling (0 – no scaling to 2 = scales with significant peeling) and total score as a sum of scores in all categories. Lower score implies better condition.
At the end of study period (3rd visit), the patient assessed characteristics of ALLERGIKA ®-Eyelid cream – its spreadability, greasiness, adhesiveness, fragrance and shine at the scale from 1 to 5. Lower score represents more positive assessment (1 = the best assessment, 5 = the worst assessment).

Applied statistical methods
Qualitative variables were processed with absolute and relative frequency distribution. Quantitative variables were processed with descriptive statistics – average, standard deviation (SD). Differences between IGA and PGA assessment of individual characteristics and in between the visits (in total) were tested with Wilcoxon non-parametric text (due to a lower number of patients in the study). Chosen level of significance was set at $\alpha = 0.05$.

Characteristics of patients
26 patients were enrolled into the study. Four patients did not comply with the entry criteria (willingness to cooperate actively in the study and come to control visits), therefore they were not enrolled into evaluation. Total number of patients in the study was 22, of those 4 (18%) men and 18 (82%) women. Recruited patients were between 25 to 79 years with the average of 44 years (SD 13). Patients could suffer from one of three diagnosis defined in the protocol. Atopic eczema was diagnosed in 11 patients (50%), allergic contact eczema in 9 (41%) patients and irritant contact dermatitis in 2 (9%) patients. Patients were divided into three groups depending on the length of the disease in years (11; 50% of patients), months (9; 41% patients) or weeks (2; 9% patients). 14 patients (64%) confirmed allergy, of that in 10 of them (71%) allergy was linked to eyelid eczema. Patients with confirmed allergy had their oversensitivity confirmed through skin tests (100%) and antigen tests (64%). One patient reported allergy that was yet not confirmed but was linked to eyelid eczema.. The rest of the patients 7 (32%) did not report allergy, while some of them were tested with negative results. Most frequent allergy was food allergy (10.45%); pollen (6.27%); metal (5.23%); chemicals (5. 23%) and mites (4. 18%). Some of the patients reported also dust and medication allergy.

Treatment of patients
At the beginning of the study period, the patients started to apply ALLERGIKA®-Eyelid cream. Simultaneously, they used antihistamines: 14 (64%) at the first, 11 (50%) at the second and 6 (30%) patients at the third visit; oral corticosteroids: 1 (5%) patient at the introductory visit, with no follow up use at subsequent visits; local non-steroid anti-inflammatory ointments and pastes: 4 (18%) at the introductory, 1 (5%) at the second and 1 (5%) patient at the third visit. The patients with condition requiring corticosteroid treatment were not enrolled into the study. One of the patients ceased to use ALLERGIKA ®-Eyelid cream due to worsened condition that required local use of topic corticosteroid.

Results
Decline in the total score assessed by dermatologists throughout the study period was statistically significant – from 4.1 ± 1.9 at the introductory visit to 2.2 ± 1.3, resp. 1.0 ± 1.1 at the visit after seven or 21 days ($p = 0.002$ for comparison of the second and introductory visit; $p < 0,001$ for comparison of the third and introductory visit). Through the study period, significant decline was also observed in individual categories (erythema, skin dryness, scaling).
Decline in total score of patients' assessment throughout the study was statistically significant: from 4,0 ± 1,9 at the introductory visit to 2.1 ± 1.2, or 1.1 ± 1.2 at the visit after 7 or 21 days ($p < 0,001$ for comparison of the second and introductory or third and introductory visit; $p = 0.003$ for comparison of the third and second visit). Significant decrease in assessment was also observed in individual characteristics (erythema, skin dryness, scaling).
The patients most positively assessed adhesive or non-adhesive characteristics of ALLERGIKA®- Eyelid cream (1.1 ± 0.3), fragrance (1.1 ± 0.3), its spreadability (1.3 ± 0.6). Shine and greasiness were assessed relatively neutrally (2.7 ± 1.0, or 3.3 ± 0.7).

Table 2 IGA assessment (average ± SD)

	First visit	Second visit (7th day)	Third visit (21st day)
Erythema	1.7 ± 0.8	1.2 ± 0.6 *	0.7 ± 0.6 **
Skin dryness	1.6 ± 0.8	0.7 ± 0.6 **	0.3 ± 0.6 **
Scaling	0.7 ± 0.6	0.3 ± 0.5 *	0.1 ± 0.2 *
Total	4.1 ± 1.9	2.2 ± 1.3 *	1.0 ± 1.1 **

* $p < 0,05$; ** $p < 0,001$ in comparison with the first visit

Table 3 PGA assessment (average ± SD)

	First visit	Second visit (7th day)	Third visit (21st day)
Erythema	1.7 ± 0.8	1.1 ± 0.7 *	0.7 ± 0.6 **
Skin dryness	1.5 ± 0.9	0.8 ± 0.6 *	0.4 ± 0.7 **
Scaling	0.7 ± 0.6	0.2 ± 0.4 *	0.1 ± 0.2 **
Total	4.0 ± 1.9	2.1 ± 1.2 **	1.1 ± 1,2 **

* p < 0,05; ** p < 0,001 in comparison with the first visit

Table 4 Assessment of ALLERGIKA®-Eyelid cream by patient (average ± SD)

Spreadability	1.3 ± 0.6
Greasiness	3.3 ± 0.7
Adhesiveness	1.1 ± 0.3
Fragrance	1.1 ± 0.3
Shine	2.7 ± 1.0
Total	9.5 ± 1.7

Discussion

Dermatovenerologists and ophthalmologists often see various forms of eyelid inflammations. It is often very difficult to differentiate causes of erythema, edema, pain and itching. This study offers an overview of characteristics of the most common dermatitis that can affect eyelids, e.g. irritant contact dermatitis, allergic contact dermatitis and atopic dermatitis. Our overview may be used in differential diagnostics aimed at identifying the triggers of the disease. In treatment of acute and chronic dermatitis we examined efficacy of emollients with the aim to avoid the use of local topic corticosteroids due to their adverse side effects.

The most frequent condition diagnosed in our study was atopic dermatitis. Previous retrospective studies of patients with eyelid dermatitis consistently prove that acute irritant contact dermatitis has a higher prevalence than other diagnoses like periocular atopic dermatitis, periocular airborne contact dermatitis and irritant contact dermatitis (5).

Comparative study of physical and chemical characteristics and efficacy of emollients describe this type of treatment as effective intervention in prevention and healing of irritated skin. However, it has not proven itself effective in broad spectrum. Simultaneously, with more frequent hydratation of stratum corneum hydrophilic allergens are able to penetrate the skin more easily (11).
Applying emollient ALLERGIKA® -Eyelid cream in patients with low and mild forms of dermatitis on eyelids leads to significant decline in erythema, xerosis and desquamation. Apart from the parameters assessed through protocols (IGA,PGA), we have observed a significant decline in eyelid puffiness in most of the patients. In two cases patients observed worsened skin condition after the first application of the emollient.
ALLERGIKA®-Eyelid cream helps to mitigate symptoms of dermatitis, restore disrupted skin barrier and delay potential relapses. Still, attention must be paid to potential intolerance of som of the cream ingredients by a patient, even if most of the common irritants are not contained.

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Literature

1. **Benáková N.** ***Ekzémy a dermatitídy, 2. rozšírené vydáni.*** **Praha, Czech Republic: MAXDORF, 2009:184**
2. **Wolff a kol., inflammatory disorders based on T-Cell reactivity and dysregluation: 135-157** ***Fitzpatric's Dermatology in general medicine, Seventh edition.*** **United States of America: Mc Grw Hill, 2008:**
3. **Leonard J.N., Dart J.K.G, The skin and the eyes: 67.1-67.32 In: Burns T., Breathnach S., Cox N., Griffiths Ch.** ***Rook's textbook of dermatology*** **4 volume set, 8th ed., Oxford, United Kingdom: Wiley-blackwell,, 2010: 4362**

4. **Amin K.A., Belsito D.V. , The aetiology of eyelid dermatitis: a 10-year retrospective analysis, In *Contact dermatitis 2006, Dostupné na internete: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1600-0536.2006.00927.x 280-285***
5. **Temesvári E., PónyaiG., Periocular dermatitis: a report of 401 patients, In JEADV, Feb. 2009, Available on internet: https://onlinelibrary.wiley.com/doi/10.1111/j.1468-3083.2008.02949.x, 124-128**
6. **Oh J.E., Lee H.J., Choi Y.W, Metal allergy in eyelid dermatitis and evaluation of metal contents in eye shadows, In JEADV, Sept. 2016, Available on internet: https://onlinelibrary.wiley.com/doi/10.1111/jdv.13646**
7. **Feser A., Mahler V., Periorbital dermatitis: Causes, differential diagnosečs and therapy, In JGSD, Mar. 2010, Available on internet: https://onlinelibrary.wiley.com/doi/10.1111/j.1610-0387.2009.07216.x**
8. **Bourke J., Coulson I. English J., Guidelines for the management of contact dermatitis: an update, In BJD, May 2009, Available on internet: https://www.ncbi.nlm.nih.gov/pubmed?term=19302065**
9. **Mowad CM., Anderson B., Scheinman P., Pootongkam S., Allergic contact dermatitis: Patient diagnosis and evaluation, In JAAD, June 2016, Available on internet: https://www.ncbi.nlm.nih.gov/pubmed?term=27185421**
10. **Yokota M., Maibach HI., Moisturizer effect on irritant dermatitis: an overview, In Contact dermatitis, Aug. 2006, Available on internet: https://www.ncbi.nlm.nih.gov/pubmed?term=16930228**
11. **Eichenfield LF. A kol. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis, In JAAD, feb. 2014, Available on internet: https://www.jaad.org/article/S0190-9622(13)01095-5/fulltext**
12. **Chen J.J. a kol, Atopic keratoconjuctivitis: a Riview, In JAAD, March. 2014, Available on internet: https://www.jaad.org/article/S0190-9622(13)01150-X/fulltext**
13. **Wolf R., Orion E., Tuzun Y., Periorbital (eyelid) dermatides, In Clinics in Dermatology, Jan-Feb 2014, Available on internet: https://www.sciencedirect.com/science/article/pii/S0738081X13001028**

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