Ocular allergic contact dermatitis from topical drugs

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Purpose of review
Ocular allergic contact dermatitis is a common yet challenging and frequently misdiagnosed condition. Inappropriate or delayed treatment can contribute to a variety of clinical symptoms such as tearing and itching with signs such as ptosis and cicatricial ectropion, resulting in deterioration of disease, for which the topical medication was originally prescribed to resolve.

Recent findings
Understanding previously unrecognized pathogenic mechanisms involving ocular contact dermatitis has driven new approaches to control the inflammatory process by neutralizing inflammatory mediators and their receptors.

Summary
Early diagnosis and removing the antagonizing substance is crucial to manage ocular contact dermatitis. Steroid therapy is usually required to reduce symptoms. As ocular allergic dermatitis often develops in patients using drugs for chronic conditions that necessitate chronic application, it may be difficult at times to discontinue or replace the offending agent.

Keywords
allergic contact dermatitis, ophthalmic medication allergy, topical antibiotic allergy

INTRODUCTION

Allergic contact dermatitis (ACD) are common inflammatory skin diseases which occur at the site of recurrent contact with a nonprotein chemical molecule [1–6]. A relatively difficult and underdiagnosed condition by eye care practitioners, when left untreated the clinical signs and symptoms can cause enough discomfort to lead to noncompliance in patients [7–10].

In this review, we will include the current information involving ocular contact allergic dermatitis. The characteristics of ACD will be outlined, in contrast to those of irritant contact dermatitis. The epidemiology, differential diagnosis, pathogenesis, and clinical presentation of ACD will be discussed. Particular attention will be devoted to allergies to various topical ophthalmic drugs, either the preservative or other inactive ingredients, or the active drug of various drug categories, followed by discussion of the current management options of contact dermatitis.

ALLERGIC CONTACT DERMATITIS

The main differential diagnosis of ACD is chronic dermatitis in the eyelids which includes atopic dermatitis and seborrheic dermatitis (Table 1). These two entities have distinct clinical features, and usually lack history of chronic topical drugs used in the ocular surface and lids.

Contact dermatitis is divided into two forms: irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD is the more frequent at a ratio of 4:1 to ACD [11–14,15▪▪]. There are many similarities between the two conditions and some distinctions (Table 2). ICD is caused by a local toxic reaction to an irritant, commonly in the form of alkali, acid, solvent, or soap [11–14,15▪▪]. ACD manifests a delayed allergen-specific type-IV hypersensitivity reaction that is a result of skin touching and reacting to a foreign substance after previous exposure and consequential immunological sensitization [16,17],

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Curr Opin Allergy Clin Immunol 2020, 20:528–538
DOI:10.1097/ACI.0000000000000677

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KEY POINTS

- Allergic contact dermatitis is a delayed allergen-specific hypersensitivity occurring after at least one repeat encounter. This type of reaction comprises 20% of the total cases of contact dermatitis and is often overlooked by eye care practitioners.
- Several ophthalmic topical medications have either active or inactive ingredients which can develop into allergic contact dermatitis. Allergy to the active ingredients is far more common than to preservatives.
- Management of the allergy is primarily removal of the offending agent, when possible. This is often quite a challenge as accurately identifying the source can be a slow procedure if the allergen is not a part of the standard patch test kits.

often in the form of metals, preservatives, or fragrances [12,18–20]. It is the leading cause of allergic periorbital dermatitis [19]. Both forms evolve from an acute to a chronic stage and exhibit similar cutaneous responses from both a histological and clinical perspective [21]. Differentiating between irritant versus allergic response is important as many of the ingredients in ophthalmic solutions are known to be irritants [13,14,22,23]. The three most common sources of eyelid contact dermatitis are cosmetics, topical ophthalmic medications, and contact lens solutions [16,17].

Periorbital ACD is associated with topical ophthalmic medications in all formulations including drops, ointments, creams, cosmetics, or other skincare products and is a condition often overlooked [12,19,22,23]. As the eyelid skin is particularly thin, 0.55 mm [18], it is more susceptible to allergen penetration and sensitization than most areas of the body [16,17]. It is exposed to airborne irritants, tends to be touched frequently, and is a popular site for many products [17,24–29]. Factors affecting the allergic reaction include the attributes of the allergen, its concentration, frequency, and amount of exposure time.

The initial response to the foreign substance in ICD can range from weeks to months depending on the irritants' potency, whereas in ACD, it occurs much more quickly, between 48 and 96 h [12–14,15▪▪,30]. Diagnosis of ICD is by way of exclusion, and there is no specific diagnostic test, which makes it a difficult and sometimes time-consuming process [21]. ACD can be diagnosed with patch testing in conjunction with a thorough patient history [12–14,15▪▪,30].

In ICD the lesions tend to stay localized, not spreading beyond the area of contact whereas in ACD, the skin affected may go well beyond the margins of the original contact of the offending material [12–14,15▪▪,30]. Treatment for both ICD and ACD patients is similar [12–14,15▪▪,30], primarily distancing the trigger or allergen, antiinflammatory therapy, and moisturizers or ointments to restore skin barrier function [13,14,15▪▪,30]. Eczematous lesions affecting the eyelids or periorbital skin are a common sign of ACD [13,14], whereas conjunctivitis is a rare clinical manifestation [22,23].

Table 1. Principal differential diagnostic for allergic contact dermatitis

Dermatitis	Differentiating characteristic
Atopic dermatitis	Personal or family history of atopy
	Small vesicles
	Early age of onset – early childhood
	Typical distribution
	Glazed, parched, or scalded appearance
	Sharply circumscribed dermatitis
	Patch testing negative
	Intensely pruritic and itching prodrome
	Persists for 2–3 weeks and then resolves by involution and desquamation
	Distribution: areas with sebaceous glands
	Scalp, periauricular, face (medial eyebrows, glabella, nasolabial folds), presternal trunk, interscapular
	Blepharitis common
	Dandruff appears to be a precursor
Seborrheic dermatitis	Blepharitis can appear
	Dandruff appears to be a precursor
	areas with sebaceous glands
	Scalp, periauricular

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Table 2. Comparison of characteristics of irritant contact dermatitis and allergic contact dermatitis

	Irritant contact dermatitis	Allergic contact dermatitis
Ratio of contact dermatitis	Approximately 80% of contact dermatitis cases	Approximately 20% of contact dermatitis cases
Type of allergic reaction	Consequence of a local toxic encounter	A delayed type of hypersensitivity of T-helper 1 (Th1) response
Onset	Usually prompt reaction- minutes to hours, but depends on irritants potency	Delayed reaction, 48–96 h
Stages	Acute, subacute, chronic	Acute, subacute, chronic
Number of contacts to elicit dermatitis	Affects at first presentation	Prior sensitization, or contact, required
Agent	Water, soaps, alkalis, acids, solvents	Allergens, metals, preservatives, fragrances
Repeat reaction	Repeated or prolonged exposure, dose-dependent required to elicit reaction	Small quantity of allergen sufficient for a response
Cross-reaction	No cross-reaction	Possible cross-reaction
Symptom	Burning sensation pronounced	Burning sensation not as pronounced
Affected area	Lesions localized to area of contact	Localized but can expand beyond margins
Diagnosis	Patch test negative	Patch test positive
Therapy	Avoidance of triggers, antiinflammatory therapy, restoration of reduced skin barrier function with moisturizers or ointments	Avoidance of triggers, antiinflammatory therapy, restoration of reduced skin barrier function with moisturizers or ointments

Although most of the cases of ACD from eye medication were usually attributed to the active ingredients, some of the inert additives can be the cause as well [13,14,15▪▪].

EPIDEMIOLOGY

The cause of periorbital dermatitis in the elderly tends to be topical medications. Young patients' sensitivity is usually to cosmetics or skincare products which cause skin atopy and allergies [20,22].

The prevalence of adult dermatitis is much higher in females than males (87.6%), approximately half the affected are between the ages of 40–59 years old (45.9%) and tends to decrease with age [22]. Study of prevalence of atopic dermatitis among different ethnicities in 60 countries found it occurs more often in Asian and Black individuals than Whites [31].

In children, atopic dermatitis is the most prevalent skin disorder but there is little information on what the percentage of contact allergy is. Information in the literature specifying contact allergies related to ophthalmic drugs is scarce, except to atropine 1% [32]. In another study comprised children diagnosed with atopic dermatitis, the percentage of contact allergy was 45.2% of the children [32,33]. The greatest proportion of positive patch tests were in the youngest group of children as well as the overall highest detection of contact allergy [32,33]. This was attributed to the immaturity of the epidermal barrier in the first years of life [34].

PATHOGENESIS OF ALLERGIC CONTACT DERMATITIS

The patient comes in contact with a chemical, which penetrates the stratum corneum and is processed in the epidermis by Langerhans cells. Antigen–Langerhans cells leave the epidermis to the local lymph nodes where they present the antigens to CD4+ cells [35–38,39]. The T cells that respond are stimulated via a complex process to propagate into memory and effector T cells [35,40–43]. It is the ensuing subsequent exposures of the original allergen to a T-cell environment already prepared to react, followed by the release of cytokines and chemotactic factors that generates the allergic response (Fig. 1) [12,13,15▪▪,19,30]. After that initial sensitivity, only a small amount of the chemical is necessary to create the typical reaction that occurs 48–96 h following reexposure [12].

CLINICAL MANIFESTATIONS

Inflammation can involve the eyelid margins, skin, conjunctiva, and eyelids in isolation or associated with a chronic conjunctivitis, keratoconjunctivitis, or other systemic manifestations [44–47]. Delaying treatment can cause secondary complications such as tearing, ectropion, ptosis, and an increase of dermatochalasis [12,18–20,22,23]. Pruritus, erythema, edema and scaling of the periorbital region are some of the most common clinical signs of contact dermatitis (Fig. 2) and identifying and

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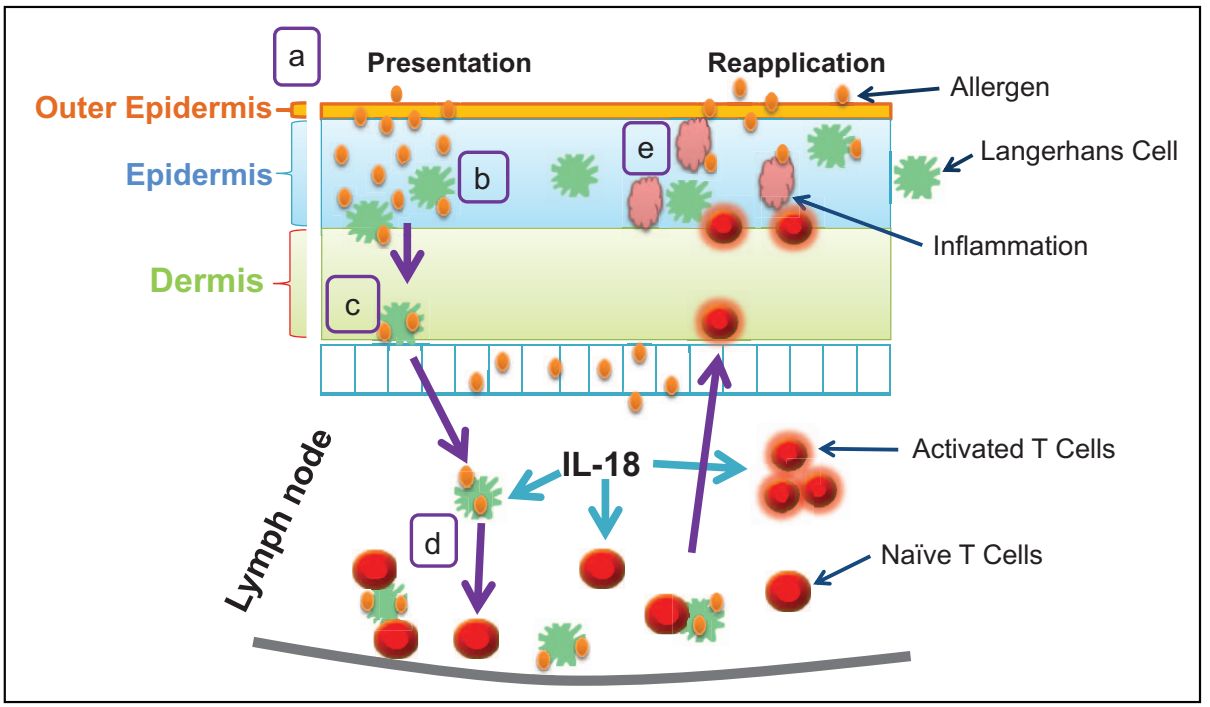

FIGURE 1. The allergic contact dermatitis inflammatory response. (a) The allergen presents and comes in contact with the outer epidermis, (b) then is processed in the epidermis by Langerhans cells. (c) Langerhans–allergen cells migrate via the dermis to local lymph nodes and (d) introduce the antigen to naïve T cells. (e) These now-activated T cells are prepared to react swiftly at the next encounter of the allergen, followed by release of cytokines and chemotactic mediators, generating the allergic inflammation.

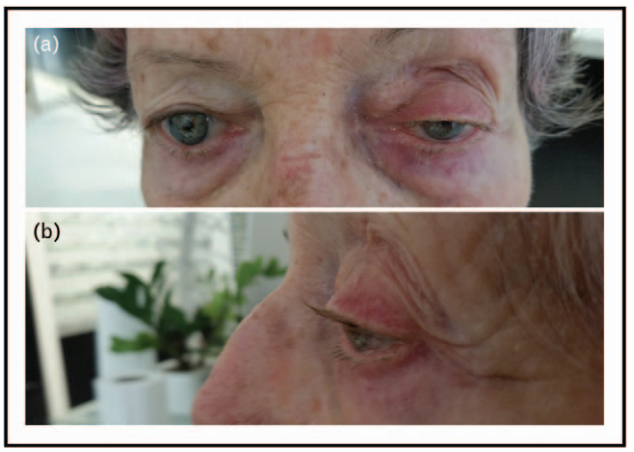

FIGURE 2. Clinical presentation of a mild ACD. (a) A 69-year-old female suffering from allergic ocular contact dermatitis in both eyes, more severe in the left eye. She had used Systane eye drops OU and Zylet eye drops in her left eye continuously for a few months. Her symptoms included itching, burning and tenderness, and signs included rash, ptosis, with dry and cracked skin. (b) Side view of the left eye demonstrating mild erythema with absence of edema over the eyelids and periorbital area (original images courtesy of Nir Erdinest with permission from patient).

removing the offending element is the first line of management [12–14,15▪▪,19,22].

ACD has three clinical stages: acute, subacute, and chronic. Acute ACD signs includes erythema, edema, pruritus, and sometimes vesiculation [12, 18–20,22,23].

The next stage can be considered a transitional stage which transpires when there is an ongoing exposure, called subacute ACD. The characteristic presentation is erythema, crusts, and hyperkeratosis. As the disease progresses to chronic dermatitis, acute exudative inflammation decreases but the skin thickens, fissures develop, and lichenification begins [12,18–20,22,23].

DIAGNOSIS

Patient history is the key to finding the source of inflammation [48–50]. Particular attention must be focused on work environment, hobbies, frequency and length of exposure to metals, cosmetics, topical medication, and history of sensitivity in the past [5,16,17,35]. Avoiding the suspicious allergens is advised and then following the skin reaction after elimination can help with diagnosis [48–50]. Patch testing, where the skin is exposed to a suspected

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allergen and observed for signs of an allergic reaction, is considered the gold standard for diagnosis and has a sensitivity of 70% and a specificity of 80% [2,26,51].

DESENSITIZATION AND TOLERANCE

ACD is essentially the result of a delicate balance between effector and regulatory mechanisms of the immune system [52,53]. Regulatory cells are not a single type of subpopulation of T cells [33]. It is presumed that with a predominant effector phenotype for a particular allergen, any other phenotype can act as regulatory cells [54]. Early data suggest that type-2 cytokine-producing cells may be the most prominent regulatory cells in ACD, as allergic contact hypersensitivity was enhanced and tolerance reversed with precisely timed treatment with cytostatic drugs [33,55]. Preferential, stable, allergen-specific stimulation of regulatory cells given to nonprimed patients with contact allergens has sometimes been effective in developing active tolerance to an offending agent [33,56]. The idea that active suppression is possible was demonstrated in experiments using animals where allergen-specific tolerance built up in one animal was transferred by lymphoid cells from tolerant to naive animals [33,35,54].

Local desensitization was attempted and achieved by repeat allergen application to the same skin site. However, this local desensitization was rapidly (within 1 week) lost after cessation of allergen exposure [35,57]. Both clinical conditions and research demonstrated that complete and persistent tolerance can only be induced prior to contact with the sensitizing allergen [33,58]. In ACD, the mechanisms underlying specific desensitization probably depend on direct antagonism of allergen with effector T-cell function, by blocking or downregulating T-cell receptors, but as the onset of desensitization is immediate, no suppressor mechanisms can be involved at that early stage [33,35,56,59]. A permanent reversal of existing ACD in healthy individuals has not yet been achieved. Defined cellular interaction molecules and mediators are encouraging targets for future antiinflammatory therapies, some of which have entered clinical trials [33,35].

ALLERGIC CONTACT DERMATITIS TO SPECIFIC OPHTHALMIC MEDICATIONS

Although ophthalmic medications may be responsible for up to 20% of ACD, it is difficult to diagnose and to determine the agent responsible as these drugs have both active and inactive ingredients with allergen capability [60–64]. Although patch testing is the standard first-line diagnostic tool, there are a few problems using this method for ocular periorbital allergies [33]. The test is performed on the back which is much thicker skin than that of the eyelids [65]. An additional challenge presented in the literature is the numerous reports of false-negative results from patch tests to ophthalmic drugs [3,15▪▪]. It is recommended to test the actual ophthalmic medication in addition to the standard ophthalmic tray available for patch testing as many chemicals in ophthalmic compositions are not a part of the commonly available kits [15▪▪,66,67].

ALLERGENIC TOPICAL OPHTHALMIC MEDICATIONS

We have grouped here the primary known to date allergenic components in topical ophthalmic medications in their respective drug classifications. In order of decreasing frequency in published studies, the most common drugs reported as potent sensitizers are antiglaucoma agents, mydriatics, antiallergics, and preservatives. Others include antibiotics, antivirals, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) (Table 3).

GLAUCOMA MEDICATIONS

A common cause of allergic dermatitis is sensitivity to topical glaucoma medications [68,69]. These are classified as β-blockers, α-adrenergic agonists, calcium anhydrase inhibitors, prostaglandin analogs, and cholinergics. Both the active ingredient and the preservative can be the cause for ACD. The concern is that removing the offending agent and using a topical steroid in these patients, even temporarily, can have serious consequences [14]. Prostaglandin analogs have relatively low local adverse reactions [68,69]. Dorzolamide hydrochloride has few reports of periorbital dermatitis, conjunctivitis, or both [68,69]. Parasympathomimetics seem to be virtually nonirritants as only a trace of patients in the literature has confirmed reports of contact dermatitis [68,69]. β-Blockers have shown positive skin reaction test in 12.9% of the patients using the drugs, the most frequent reactions were to timolol, metipranol, and levobunol [70].

There are reports of cross-reactivity between the various β-blockers [68,69]. Cross-sensitivity has been demonstrated between befunolol and carteolol, betaxolol and timolol, timolol and levobunolol, and befunolol and levobunolol [71–73]. In the pediatric population, treatment for infantile hemangioma with timolol can present with ACD [74]. The use of apraclonidine, a potent α-adrenergic agonist

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Table 3. Allergic contact dermatitis triggered by ophthalmic medications

Main medical treatments	Treatment group	Allergen-positive patch test reactions
Eye allergies	Antihistamines	Ketotifen [130] Pheniramine maleate [131] Diphenhydramine [132]
Bacterial *eye* infections	Antibiotics	Tobramycin [15▪▪] Vancomycin [133] Gentamicin [15▪▪] Neomycin [62] Sodium colistimethate [134] Metronidazole [132,135] Azithromycin [60,61]
Inflammation	Corticosteroids	Hydrocortisone [15▪▪] Amcinonide [136] Prednisolone acetate [15▪▪] Dexamethasone [15▪▪] Hydrocortisone acetate [15▪▪] Budesonide [137]
Glaucoma	β-Blockers	Timolol [63,74,138,139] Betaxolol [64,140] Carteolol [139] Levobunolol [64] Brimonidine [76]
	Prostaglandins	Latanoprost [141]
	Carbonic anhydrase inhibitors	Acetazolamide [142] Dorzolamide [64,143]
	A2-adrenergic agonists	Apraclonidine [144]
	Rho kinase inhibitors	Ripasudil Hydrochloride Hydrate [75]
	Sympathomimetic	Dipivefrine [64,145] Apraclonidine [64] Apraclonidine [144] Brimonidine [64]
	Parasympathomimetics	Pilocarpine [64]
Inflammation	NSAID	Diclofenac sodium [146]
Eye surgical *and* procedures	Anaesthetics	Phenylephrine [15▪▪,147] Atropine [15▪▪,34] Proparacaine [148] Neosynerphin [147] Epinephrine [64,140]
Others	Preservatives	Benzalkonium chloride [15▪▪,62,149] Thimerosol [15▪▪,62] Phenylmercuric borate [15▪▪] Sodium bisulfite [15▪▪]
	Vehicle, humectant, and emulsifier	Propylene glycol [150]
	Surfactant	Sodium lauryl sulfate [151]

used in the management of open angle glaucoma and ocular hypertension, was discontinued because of the high incidence of ACD, 48% in one series [75]. Brimonidine, a highly selective α-2 adrenergic agonist, shows lower allergy rates than apraclonidine because of its higher oxidative stability [76]. ACD from carbonic anhydrase inhibitors and prostaglandin analogs is not common. There are few reports of cases of reaction to dorzolamide [77,78] and latanoprost [79], and a lone report of reaction to bimatoprost [80]. There are no reports of ACD to brinzolamide or travoprost. In glaucoma management, there is a rising trend to prescribe rho kinase inhibitors which decrease intraocular pressure (IOP) by increasing outflow. Kusakabe *et al.* [75] reported a single such ACD case from use of Glanatec 0.4% solution.

Sympathomimetics are medications often used prior to Yttrium aluminium garnet (YAG) capsulotomy in combination with the patients' maximum tolerated glaucoma medication to prevent increased IOP after the procedure. It is usually used as a short-term therapy as systemic and local adverse reactions

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are common. The rates of adverse reactions vary in reports when discussing both different types of sympathomimetics and even within the same category. For example, reports of allergic reaction to brimonidine tartrate vary from 4.8 to 9% to over 17% of patients [68,69].

MYDRIATICS AND CYCLOPLEGICS

Mydriatics are frequently used in ophthalmology to allow for a proper examination and treatment of diseases of the posterior segment by dilating the pupil. Phenylephrine is a known source of ACD and responsible for about 30% of cases [81]. Though extensively reported in adults, reactions in children are rare [82]. Phenylephrine cross-reacts with pseudoephedrine, found in many over the counter treatments for the common cold [83]. Reactions to phenylephrine can be very severe and debilitating. Kato *et al.* [84] described periocular ACD to phenylephrine presenting as a fulminant keratoconjunctivitis with dense pseudomembranes in a 51-year-old Japanese woman. Allergic reactions to tropicamide are rare and only three reports are found in the literature [85–87]. Of note is the increasing incidence of ACD in patients undergoing intravitreal injections. The majority of patients react to components of drugs used before the procedure, 56% of which are because of phenylephrine [88].

In recent years, there has been a spike in the use of atropine, a nonselective muscarinic antagonist, for the prevention of childhood myopia progression. Overall, 2.9% of these children develop an allergy, usually in children using high dose (0.5–1%) atropine [89].

ANTIALLERGIES

Antiallergic medications, paradoxically, can infrequently cause contact hypersensitivity symptoms [68,69]. Antihistamines and mast cell stabilizers are used in the treatment of patients with ocular allergy and suspicion should be raised when symptoms worsen with use, or when there is a new onset of periocular inflammation [90]. A decrease in ACD reports has been felt with newer antihistamines. In the past sodium cromoglycate, chlorpheniramine and amlexanox have all been implicated to cause ACD [91–93]. Recent allergenic drugs, though infrequent, include olopatadine [90] and alcaftadine [94]. Epsilon aminocaproic acid (EACA) is an antifibrinolytic agent with antiinflammatory properties used in Japan since the 1980s as an antiallergy drug. Its use was stopped after several reports of allergic reactions but it seems to be reemerging [95].

PRESERVATIVES

Preservatives are important inactive additives to many ophthalmic medications which delay decomposition and prevent contamination of the drug [25,96,97]. Since 1969 when Raymond and Gross reported on ACD caused by Ethylene diamine tetraacetic acid (EDTA) in eyedrops [98], it is known that preservatives are a common allergen in ophthalmic preparations. Some can cause adverse reactions particularly when dealing with frequent or long-term therapy but usually the allergic reaction is to the active ingredient [68,69]. The most common preservatives that have been reported to cause ACD in the literature are benzalkonium chloride (BAC), EDTA, parabens, thimerosal, phenylmercuric salts, metabisulfites, and chlorobutanol [68,69].

Thimerosal is rarely used today as a preservative and most ophthalmic preparations use BAC which has low allergenicity. There are several reports of reactions to BAC in topical preparations for the skin, but there are no case reports of BAC-related ACD from eyedrops. Only 1.1–1.6% of patients with periorbital dermatitis develop a type IV sensitivity reaction to 0.1% BAC, the majority showing weak reactions [15▪▪,19].

Nonpreserved ophthalmic preparations are increasingly available which help reduce toxicity and reactions and simplify identification of the allergen in cases of dermatitis [68,69].

ANTIMICROBIALS

Antimicrobials can cause mild to life-threatening allergic reactions. Pertaining to ocular contact dermatitis, it is a rare occurrence from most compounds as many antibiotics are only prepared for systemic use. Aminoglycosides like tobramycin, neomycin, kanamycin, and gentamycin are the most common antibiotics in ophthalmic preparations causing ACD [99]. Reactions to chloramphenicol are less common now and though underreported can be severe in nature.

There is just one report of ACD to azithromycin dihydrate eyedrops in a 76-year-old following cataract surgery [100]. Other antibiotics that cause ACD include polymyxin B sulfate, bacitracin, and vancomycin [27]. Fradiomycin sulfate (neomycin) ointment is available in Japan in combination with methylprednisolone or betamethasone and was recently reported to be a significant cause of ACD in this population though many physicians continued prescribing it [101]. Sulfonamide antibiotics are known to cause systemic delayed-type hypersensitivity reactions like Stevens–Johnson syndrome, but no reports from ophthalmic preparations were published, probably as they are not commercially available. Over the last decade, voriconazole has gained

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popularity in the treatment of fungal keratitis and can cause ACD as reported by Sahay *et al.* [102] in two patients.

ANTIVIRALS

Topical antivirals have been used for many years in the treatment of herpes simplex and varicella-zoster keratitis. Most reports on idoxuridine are from the 1970s and 1980s with up to 2.3% of users presenting with ACD [29,60,64,66,103,104]. Few reports are available for trifluridine and patients can show cross-sensitivity to idoxuridine [66]. Documented contact dermatitis from topical acyclovir is rare and mostly involves nonocular skin though it can cause punctate keratopathy [105]. Apart from the possibility of underreporting from negligible reactions, the absence of cases may be related to the lower dosage in ophthalmic preparations (3%) compared with the 5% in other topical ointments.

ANTIINFLAMMATORY MEDICATIONS

Though counterintuitive, corticosteroid and NSAID eyedrops can cause ACD [68,69]. It must be considered in patients with periorbital inflammation who fail to improve or deteriorate following treatment. It can result from local application with eyedrops, gels, and creams or through hand-to-eye transmission after application to other sites of the body [106]. Hydrocortisone is the most common cause of ACD and a large proportion of these patients have multiple sensitivities to other active drugs, preservatives, and vehicle components [106–108]. Gilissen *et al.* [15▪▪] reported that corticosteroids were the most commonly reacting active ingredients in ophthalmic medications after antibiotics, the prominent culprits being hydrocortisone, hydrocortisone acetate, dexamethasone, prednisolone acetate, and prednisolone pivalate. ACD from NSAIDs is rare but can cause skin hypersensitivity. At least two cases of ocular allergy have been reported [68,69], most often caused by diclofenac sodium which has also been reported to have a combined reaction with indomethacin [107,109]. There are no reports on Nepafenac causing ACD.

ANESTHETICS

Anesthetic ophthalmic drugs used topically can cause an allergic reaction but generally there is no cross-sensitivity so if necessary therapy can be altered to another in the same family [68,69]. The ophthalmic anesthetics known to potentially cause contact dermatitis or conjunctivitis are tetracaine, oxybuprocaine [benoxinate], and proparacaine [68,69].

OTHER ALLERGENIC DRUGS

Several active ingredients in ophthalmic preparations have been reported to cause ACD yet their incidence is rare, with single case reports found in literature. The most recent report was of thioctic acid, a highly reductive antioxidant used in Hypromellose eyedrops for treatment of dry eye syndrome which caused periorbital swelling in a 64-year-old woman for seven months until patch testing was done with her own eye drops [110]. Cumurcu *et al.* [111] described ACD to topical mitomycin C 0.02% eyedrops used after surgical excision of invasive squamous cell carcinoma in a 63-year-old woman. Lesions appeared two days after the onset of treatment and disappeared after discontinuation and treatment with topical corticosteroids. Patch tests were positive to 0.01% Mitomycin C (MMC). Other reports were found on lanolin, pirfenoxone, *N*-acetylcysteine, bismuth, yellow mercuric oxide, resorcinol, penicillamine, and rubidium iodide [112–119]. Although tacrolimus 0.1% ointment can cause ACD [120], there are no reports involving the periocular area. One unique case of periocular ACD caused by ofloxacin was reported [121].

TREATMENT

In addition to removal of the offending agent, steroids are the treatment of choice to manage ACD, and the goal is to minimize inflammation and to reduce the symptoms and clinical manifestations before the chronic stage of the disease [68]. A retrospective study tried to determine if there was a significant disparity from diagnosis-to-cure in patients treated with various combinations of therapies. They reported that there was no significant difference between combination topical steroid and antibiotics treatment versus steroids alone, but combination of oral antihistamine and topical steroid were far more effective than monotherapy with topical steroids [122].

Patients with chronic dermatitis that do not respond to topical or systemic steroids can be treated with psoralen and ultraviolet A (UVA) treatment, narrow-band ultraviolet B (UVB) treatment, systemic treatment with immunomodulators or targeted biologic therapy such as dupilumab [68,123▪,124–129].

CONCLUSION

Allergic contact dermatitis to ophthalmic drugs may be responsible for up to 20% of the cases of ACD. The

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major issue is awareness of the possibility of ACD to topical ophthalmic drugs by practitioners, prompt recognition of the causative agent, and cessation of the offending agent. Beyond the detrimental long-term effects of dermatitis, it is important to reduce symptoms as they lead to poor compliance, followed by lower efficacy of intended treatment. Although therapy up to this point has been primarily avoidance either in a broad-spectrum fashion or isolating specific allergen, the future is turning toward development of more personalized and precise options.

Acknowledgements

The authors would like to thank Mrs. Batel Hass for her contribution in preparing Fig. 1 for this article.

Financial support and sponsorship

N.E. is grateful to the Azrieli Foundation for the award of a postdoc Azrieli Fellowship.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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The goal of this study was to map the demographic characteristics, lesion locations, and associated medical conditions of the patients with ACD caused by ophthalmic drugs and to identify the most common allergenic culprits, as well as trends in frequencies over the years. Sixteen thousand and sixty-five patients with a positive patch test reaction to an eye medication or its ingredient were investigated. For each allergen identified, the number of positive test results as compared with the total number of those in the total population, as well as trends across three eight-year periods. They concluded that ACD caused by eye medication is generally attributed to active component, but other excipient ingredients should be tested too.

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