

Allergic Contact Dermatitis to Ophthalmic Medications: Relevant Allergens and Alternative Testing Methods

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Allergic contact dermatitis is an important cause of periorbital dermatitis. Topical ophthalmic agents are relevant sensitizers. Contact dermatitis to ophthalmic medications can be challenging to diagnose and manage given the numerous possible offending agents, including both active and inactive ingredients. Furthermore, a substantial body of literature reports false-negative patch test results to ophthalmic agents. Subsequently, numerous alternative testing methods have been described. This review outlines the periorbital manifestations, causative agents, and alternative testing methods of allergic contact dermatitis to ophthalmic medications.

Allergic contact dermatitis (ACD) is a common cause of periorbital dermatitis.^{1–4} The thin epidermis of the periorbital skin renders eyelids particularly sensitive to hapten penetration and subsequent ACD.⁵ Topical ophthalmic agents represent an important group of haptens. Sensitization rates to ophthalmic medications are difficult to ascertain and likely are underreported because practitioners and patients empirically switch preparations without confirming sensitivity. Among a cohort of 1730 patients patch tested for suspected allergy to topical ophthalmic medications, 601 (35%) had a final diagnosis of ACD.⁶ Other causes of periorbital dermatitis are listed in Table 1.^{7,8}

Traditionally, skin patch testing using individual ingredients (including both active and inactive components) is used to identify responsible allergens. Substances are tested at dilute concentrations found to be nonirritating and nonsensitizing. Obtaining pure ingredients and determining the appropriate concentration and vehicle for testing, particularly active ingredients in ophthalmics, can be challenging. Suggested concentrations are listed in Table 2; standard ophthalmic testing series have also been proposed.¹⁴

However, a large body of literature reports false-negative patch test results to ophthalmics in cases of suspected ACD. Several alternate testing methods have been reported.

This article provides an up-to-date review of ACD to ophthalmic medications with an emphasis on relevant allergens and description of alternative methods for testing beyond traditional patch testing. PubMed was used to search for articles in English using the terms “allergic contact dermatitis,” “eye drops,” “ophthalmics,” and “ophthalmology.” In addition, hand searching of published articles was performed.

CLINICAL PRESENTATION

Signs of ACD include erythema, papules or vesicles, and swelling of the periorbital region³ (Fig. 1A, B). Pruritus is strongly suggestive of contact allergy. Other features include lichenification and postinflammatory hyperpigmentation in prolonged cases.⁸ Chronic scratching may lead to secondary infection, loss of eyelashes, or change in tearing function.¹⁵

RESPONSIBLE ALLERGENS: ACTIVE INGREDIENTS

Antiglaucoma Medications

Many antiglaucoma medications are used long term and in combination with other agents to control intraocular pressure, increasing the risk for contact sensitization (Fig. 2).

β-Blockers

Allergic contact dermatitis to β-blockers is well described. Reported allergens include befunolol, betaxolol, carteolol, levobunolol, metipranolol, metoprolol, and timolol.¹⁶ De Groot et al¹⁷ reported a series of 6 patients diagnosed with ACD secondary to the β-blocker

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TABLE 1. Differential Diagnosis for Eyelid Dermatitis

Disease	Symptoms/Symmetry	Clinical Findings
ACD	Pruritus > burning May be symmetrical or unilateral depending on allergen exposure	Vesicles, erythema, induration, swelling, lichenification; positive patch test results
Irritant contact dermatitis	Burning > pruritus May be symmetrical or unilateral depending on irritant exposure	Erythema, scale, desquamation; negative patch test results
Atopic dermatitis	Pruritus Symmetrical	Inflammation, erythema, scale, lichenification; involvement of hands/flexures/nipples/neck; often associated with allergic rhinitis and/or asthma
Psoriasis	Mild pruritus Symmetrical	Clearly defined red plaques, overlying silvery-white scale; usually involves eyebrows
Rosacea	Foreign body sensation, pruritus, burning, dry eyes Symmetrical	Scaling, erythema, swelling along lid margins; scaly debris at base of eyelashes
Seborrheic dermatitis	+/- pruritus Symmetrical	Salmon-pink to orange, ill-defined, thin plaques with greasy scale; predominant involvement of eyebrows and glabella
Dermatomyositis	Often asymptomatic Symmetrical	Violaceous periorbital erythema, "heliotrope" rash; +/- proximal muscle weakness
Skin cancer	Often asymptomatic, can be tender or painful Asymmetrical	Spontaneous bleeding or ulceration
Periorbital (preseptal) cellulitis	Tender, warm Asymmetrical	Erythema, swelling, +/- erosion, ulceration, lymphadenopathy

in their eye drops, including metipranolol, levobunolol and timolol. A retrospective review by Jappe et al¹⁸ of 332 patients patch tested to topical antiglaucoma drops reported a 13% positivity rate, most commonly to timolol, metipranolol, and levobunolol. Interestingly, none of these patients reacted to inactive ingredients. Sensitization rates to β -blockers are likely higher than reported due to infrequent referral for patch testing, difficulty in obtaining active ingredients for testing, and false-negative patch testing results.^{17,19,20}

Cross-reactivity among β -blockers is unpredictable and seemingly random.^{21,22} Often, multiple β -blockers are patch tested to determine tolerability. If a patient has been exposed to multiple β -blockers, concomitant sensitization may occur rather than true immunologic cross-sensitization. There are 3 reports of cross-reactivity among befunolol/carteolol, timolol/levobunolol, and befunolol/levobunolol; these patients had no prior exposure to the second β -blocker, suggesting true cross-reactivity.^{23–25}

Prostaglandin Analogs

Allergic contact dermatitis to prostaglandin analogs, currently recommended as first-line treatment for glaucoma, is rare. The first report of ACD to latanoprost in 2002 described strong positive reactions [patch and repeat open application test (ROAT)] to a latanoprost 0.005% solution with a negative reaction to the vehicle.²⁶ Pérez-Rodríguez et al²⁷ reported ACD to latanoprost and levobunolol eye drops confirmed through patch testing with tolerance to bimatoprost. There is 1 report of ACD to eye drops containing bimatoprost. Although pure bimatoprost was not

available for testing, the other individual constituents of the eye drops were negative.²⁸ Beyond its use as an antiglaucoma agent, bimatoprost is also available in a solution to induce eyelash hypertrichosis. To date, there have been no reported cases of ACD to travoprost.

Carbonic Anhydrase Inhibitors

Several cases describe ACD to dorzolamide, the first commercially available topical carbonic anhydrase inhibitor used as adjuvant therapy in glaucoma to reduce production of intraocular fluid. Delaney et al²⁹ described a cohort of 14 patients who developed periorbital dermatitis after initiating dorzolamide eye drops. Although 8 cases resolved with discontinuation of dorzolamide, 6 did not until their concomitant β -blocker was discontinued. Patch testing was negative in all 6 patients who underwent testing. Two patients were rechallenged with their dorzolamide eye drops; both experienced recurrence of eyelid dermatitis.²⁹ Positive patch testing to dorzolamide has been described in an additional 6 reports.^{30–35} Kluger et al³⁶ described an interesting case of systemic contact allergy to dorzolamide eye drops, with eczematous plaques on the patient's abdomen and right eye during unilateral right eye drop use. The patient's abdominal and unilateral periorbital plaques flared during eye drop ROAT.³⁶

Adrenergic Agonists

Phenylephrine, an α -1 agonist used as a mydriatic agent during examinations and in the treatment of glaucoma, is an important sensitizer. Landeck et al⁵ reported a 3% sensitization rate among

TABLE 2. Ophthalmic Causes of Periorbital ACD

Hapten	Suggested Patch Test Concentrations/Vehicles*
Active ingredients	
β-Blockers	
Befunolol	1% aq
Betaxolol	1%–5% aq
Carteolol	1% aq
Levobunolol	1% aq
Metipranolol	2% aq
Metoprolol	3% aq, 10% pet
Timolol	0.5% aq, 0.5% pet
Prostaglandin analogs	
Latanoprost	0.005% in common solution
Bimatoprost	0.003% aq
Carbonic anhydrase inhibitors	
Dorzolamide	0.1%–1%–2% aq, 5% aq, 5% pet
Adrenergic agonists	
Phenylephrine	1% aq, 5% aq, 10% aq, 1% pet
Dipivefrine	0.5% aq, 1% aq
Brimonidine tartrate	Unknown
Apraclonidine	10% aq
Cholinergic/parasympathomimetics	
Pilocarpine	1% pet, 4% pet
Anticholinergic/antimuscarinics	
Atropine	0.5% pet, 1% pet, 1% aq
Cyclopentolate	0.5% aq
Antihistamines	
Alcaftadine	0.25% in common solution* ⁹
Pheniramine maleate	1% aq
Olopatadine	Unknown
Ketotifen fumarate	0.07% aq
Mast cell stabilizers	
Sodium cromoglycate	2% aq* ¹⁰
Artificial tears	
EAA	0.1%, 0.2%, 1%, 5%, 10% aq/1%, 3%, 6%, 30% pet* ¹¹
Nonsteroidal anti-inflammatory drugs	
Diclofenac sodium	1% pet
Antibiotics	
Gentamicin	20% pet
Neomycin	20% pet
Kanamycin	10% pet, 20% pet
Tobramycin	5% aq, 20% aq, 20% pet
Azithromycin	1% pet, 5% pet
Chloramphenicol	0.5%–10% pet
Antivirals	
IDU	0.5% pet, 1% pet
TFR	5% pet
β-Interferon	Unknown
Antiseptics	
Bismuth oxide	0.5% pet, 5% pet
Chemotherapeutics	
MMC	0.1% pet
Antioxidants	
Pirfenoxone	0.005% aq, 1% aq

TABLE 2. (Continued)

Hapten	Suggested Patch Test Concentrations/Vehicles*
Mucolytics	
N-acetylcysteine	10% aq* ¹²
Anesthetics	
Proparacaine	2% aq, 5% aq, 2% pet
Tetracaine	1% pet, 5% pet, 2% aq
Corticosteroids	
Betamethasone valerate	5% pet, 1% alc
Tixocortol-21-pivalate	0.1%–1% pet
Hydrocortisone butyrate	1% alc, 1% pet
Inactive ingredients: preservatives	
Benzalkonium chloride	0.01%–0.1% aq
Thimerosal	0.1% pet
Phenylmercuric acetate	0.01% aq, 0.05% pet, 0.1% pet
Phenylmercuric nitrate	0.01% aq, 0.01%–0.05% pet
Sodium metabisulfite	1%–5% pet, 1% aq, 2% aq, 5% aq
Chlorobutanol	Pure, 5% oo, 1% pet
Contact lenses	
Hydroxyethyl methacrylate	2% pet, 5% pet, 0.1% alc
Triethylene glycol diacrylate	0.1% pet

*de Groot¹³ recommended concentrations except as noted.

Alc indicates alcohol; oo, olive oil.

1144 patients patch tested to an ophthalmic tray. Villarreal³⁷ described 37 patients referred for skin patch testing due to adverse reactions specifically to mydriatic eye drops. Phenylephrine was the most common sensitizer, affecting 93.5% of the 31 allergic patients. Patch testing was confirmative in 68.5% of patients. Sensitivity was proven solely on conjunctival challenge in one fourth of patients.³⁷ In a separate cohort, patch testing revealed positive reactions to phenylephrine in 7 of 8 patients using phenylephrine eye drops.³⁸ Erdmann et al³⁹ found no cross-reactivity between phenylephrine and structurally related sympathomimetics (epinephrine, ephedrine) in a patient sensitized to phenylephrine from eye drops.

Dipivefrine, a prodrug of epinephrine used in the management of glaucoma, has been implicated in 3 cases confirmed by patch testing.^{40–42} Whereas Parra et al found cross-reactivity to pure epinephrine in a patient sensitized to dipivefrine, Vilaplana et al did not.^{40,41} There are limited reports of presumed ACD to the α-2 agonist brimonidine tartrate, although none were confirmed by patch testing to the active ingredient.^{43–45} A report by Swanson and Warshaw⁴⁵ described positive ROATs to eye drops and gel used for the treatment of rosacea both containing brimonidine tartrate. Finally, there is a single report of sensitivity to apraclonidine, another α-2 selective adrenergic drug, with strong reactions on patch testing to the patient's eye drops and pure apraclonidine.⁴⁶

Cholinergic/Parasympathomimetic Medications

Sensitivity to pilocarpine, a miotic agent, has been reported. Cusano et al⁴⁷ reported a patient using timolol and pilocarpine

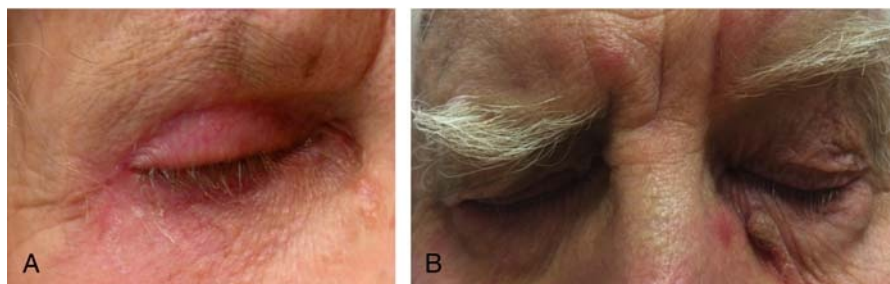


Figure 1. A and B, Clinical photographs of 2 different patients depicting periorbital allergic contact dermatitis to ophthalmics with erythema, scale, and vesicle formation.

eye drops with a 1-year history of eyelid dermatitis. Patch testing was negative to the drops and inactive ingredients. However, the patient developed erythema and vesicles with ROAT of the pilocarpine eye drops.⁴⁷ Similarly O'Donnell and Foulds⁴⁸ used alternative testing methods to illicit a reaction to pilocarpine eye drops. Traditional patch testing and intradermal testing with unpreserved pilocarpine were both negative at days 4 and 7, respectively. Prick testing with unpreserved pilocarpine resulted in a 10-mm² wheal within 30 minutes, indicating contact urticaria.⁴⁸ Finally, a separate case by Ortiz et al⁴⁹ documented positive patch tests to pilocarpine containing eye drops and pure pilocarpine.

Antimuscarinic/Anticholinergic Medications

Allergic contact dermatitis to antimuscarinic/anticholinergic medications used for ophthalmologic examinations and perioperatively has been reported. Decraene and Goossens⁵⁰ reported postoperative eyelid dermatitis after a vitrectomy with widespread body involvement. Patch testing showed strong reactions to atropine (used in the procedure) and structurally related compounds (belladonna extract, homatropine, and scopolamine) as well as unrelated tropicamide.⁵⁰ De Misa et al⁵¹ reported a case of ACD to atropine eye drops, used for

the treatment of iridocyclitis, confirmed by patch testing. Cyclopentolate, a fast-acting mydriatic agent, was implicated in a patient's eyelid dermatitis. Patch testing revealed strong reactions to both pure cyclopentolate and phenylephrine.⁵²

Anti-inflammatory Medications

Somewhat paradoxically, ophthalmic medications used in the treatment of ocular allergy may cause ACD. Currently, 13 ophthalmic antihistamines/mast cell-stabilizing agents have US Food and Drug Administration approval for the treatment of allergic conjunctivitis.⁵³ Of these, there are scattered reports of sensitization to alcaftadine, olopatadine, ketotifen, pheniramine maleate, and sodium cromoglycate.

Antihistamines

Alcaftadine, approved in 2010, is an H1 receptor antagonist. Okereke and Cohen⁹ reported the only case to date of ACD to alcaftadine in a 54-year-old woman with eyelid and facial dermatitis. The patient had a mild reaction to her alcaftadine 0.25% ophthalmic solution on conventional patch testing and a strong reaction to the same solution when tested under a scarified patch test chamber.⁹

Pheniramine maleate, formerly available by prescription, is currently available as over-the-counter eye drops for ocular allergy relief. This H1 receptor antagonist is often combined with naphazoline HCl for added antihistamine and decongestant properties. Parente et al⁵⁴ reported a case of ACD to pheniramine maleate in a patient patch tested to the individual ingredients of her pheniramine maleate and tetraizoline chloride eye drops. Additional patch testing was positive to dexchlorpheniramine maleate and chlorpheniramine maleate, both structurally related to pheniramine maleate (all alkylamine derivatives). She also reacted to diphenhydramine hydrochloride, an unrelated ethanolamine antihistamine.⁵⁴

Olopatadine, a rare sensitizer, is a relatively selective H1 receptor antagonist. Suchi et al⁵⁵ reported 2 cases of suspected ACD (not confirmed by patch testing) and periorbital depigmentation within 6 weeks of initiating olopatadine 0.1% eye drops, preserved with benzalkonium chloride. Both patients experienced resolution



Figure 2. Positive patch test results at 96 hours to patient's latanoprost, dorzolamide/timolol, and timolol eye drops.

of dermatitis with persistence of depigmentation upon cessation of the eye drops. The patients tolerated azelastine, also preserved with benzalkonium chloride.⁵⁵

There is a single report of ACD to ketotifen fumarate eye drops, an over-the-counter H1 antagonist/mast cell inhibitor. This patient had strong patch test reactions to his eye drops and pure ketotifen fumarate (0.069% aqua [water] [aq]).⁵⁶

Mast Cell Stabilizers

Finally, there are 2 reports of ACD to sodium cromoglycate, a mast cell inhibitor. Kudo et al¹⁰ reported a strong reaction on patch testing to the patient's eye drops containing sodium cromoglycate and a mild reaction to pure sodium cromoglycate (2% aq). Camarasa et al⁵⁷ used alternative patch testing methods to illicit a positive reaction after a patient had a strong reaction on patch testing to an eye drop containing sodium cromoglycate but was negative to the individual ingredients. The ROAT resulted in a vesicular dermatitis within 4 days. Further, the authors proposed a "compound allergy" as the patient developed a strong reaction to pure sodium cromoglycate + benzalkonium chloride on patch testing even though individual ingredients were negative. Perhaps benzalkonium chloride, a common irritant, allowed epidermal penetration of sodium cromoglycate.⁵⁷

Artificial Tears

Epsilon-aminocaproic acid (EAA), a fibrolysin agent produced in Japan, is added to eye drops for the treatment of allergic conjunctivitis and cataracts.^{11,58} Yamamoto et al¹¹ described 16 cases of ACD due to EAA, most of which (88%) were due to eye drops. Seven of these patients underwent patch testing, and all had positive reactions to pure EAA (0.1% to 30.0% in aq or plain petroleum [pet]).¹¹

Nonsteroidal Anti-Inflammatory Drugs

Diclofenac sodium, added to ophthalmic solutions for the treatment of intraoperative or postoperative inflammation, is a rare sensitizer. There have been 3 reports of ACD to this nonsteroidal anti-inflammatory drug.^{59–61} Miyazato et al⁵⁹ described a man who underwent cataract surgery with a postoperative course complicated by ACD. Patch testing revealed mild positive reactions to diclofenac sodium ophthalmic solution and pure diclofenac sodium (5% pet).⁵⁹ Similarly, Ueda et al⁶¹ described postoperative ACD to diclofenac sodium eye drops, confirmed with strong reactions on patch testing to the eye drops and pure diclofenac sodium (2% pet); cross-reactivity to indomethacin, but not bufexamac, was confirmed. Ketoprofen is a well-known allergen and photoallergen in nonophthalmic topical products,⁶² although we found no reports of sensitization related to eye medications.

Antibiotics

Aminoglycosides

Topical antibiotics, especially aminoglycosides, are frequent sensitizers.^{5,63–67} Landeck et al⁵ reported high sensitization rates to

gentamycin (8.1%), neomycin (5.9%), and kanamycin (4.9%) in up to 1142 patients patch tested to an ophthalmic panel. Neomycin is a common hapten included in most standard patch testing series, and cross-reactivity between neomycin and other aminoglycoside antibiotics (gentamycin, kanamycin, and tobramycin) is well described.^{63,66} Importantly, reliance on neomycin as a marker for sensitivity to this group is not sufficient, because there have been reports of positive patch results to tobramycin with negative results to neomycin.^{65,68}

Macrolides

Allergic contact dermatitis to macrolide antibiotics is exceedingly rare. Paz et al⁶⁹ reported the first case of ACD to eye drops containing azithromycin prescribed after pseudophakia surgery. Patch testing confirmed strong reactions to the single-dose unpreserved azithromycin eye drops and pure azithromycin (1%–10% pet). The patient was negative to erythromycin and clarithromycin.⁶⁹

Amphenicols

Chloramphenicol, available in eye drops and ointments for the treatment of bacterial conjunctivitis, has rarely been implicated in ACD, perhaps due to its infrequent use.^{38,70} Le Coz and Santinelli⁷⁰ reported periorbital ACD to chloramphenicol confirmed by a strong reaction on patch testing to pure chloramphenicol (5% pet). The patient also reacted to its synthetic derivative, thiamphenicol.⁷⁰

Antivirals

A review by Holdiness⁷¹ implicates ocular antiviral medications as rare sensitizers.

Idoxuridine and Trifluridine

Idoxuridine (IDU) is a topical antiviral ophthalmic solution rarely used in the treatment of herpetic keratitis because of its well-known adverse effect of chronic follicular conjunctivitis.⁷¹ Among a cohort of 132 patients treated with IDU for herpetic keratitis, 3 (2.3%) developed ACD confirmed with patch testing.⁷² Trifluridine (TFR) is less toxic and better tolerated for the treatment of ocular herpetic infections. Millán-Parrilla and de la Cuadra⁷³ described a case of ACD to TFR eye drops in a patient being treated for a herpetic eye infection. Patch testing revealed strong reactions to the eye drops and pure TFR (5%, 10% pet) but negative to IDU (0.5% pet).⁷³ Conversely, Cirkel and van Ketel described a patient sensitized to both TFR and IDU.^{74,75}

β-Interferon

Interferons are naturally occurring substances that induce an intracellular antiviral state and are used for the treatment of conjunctivitis, conjunctival papillomas, and conjunctival intraepithelial neoplasia.^{71,76} A single report by Pigatto et al⁷⁷ described ACD in a patient using β-interferon eye drops for conjunctivitis. Patch testing revealed strong reactions to the eye drops; however, individual constituents were negative. Because pure β-interferon was not

available for testing, the authors used an anti-IFN antibody to inhibit the active ingredient in the eye drops, resulting in a negative patch test.⁷⁷

Antiseptic

Bismuth oxide, used in topical ophthalmic preparations for its bacteriostatic properties, has been largely replaced by modern antibiotics. Wictorin and Hansson⁷⁸ reported a single case of periorbital ACD to a bibrocathol (bismuth oxide-tetrabromocatechol complex) ophthalmic ointment. The patient had strong reactions to pure bismuth oxide (5% pet) and the ointment on patch testing. The other constituent, tetrabromocatechol (5% pet), was negative.⁷⁸

Chemotherapeutic Agent

Mitomycin C (MMC) is an antibiotic isolated from *Streptomyces caespitosus* that undergoes metabolic activation to become a cytotoxic alkylating agent used in the treatment of ocular surface neoplasia.⁷⁹ Sensitivity to MMC is described in 2 cases. Cumurcu et al⁷⁹ described a patient treated with MMC eye drops after excision of conjunctival squamous cell carcinoma with subsequent development of periorbital contact dermatitis. Patch testing revealed a positive reaction to MMC 0.01%.⁷⁹ Among a cohort of 20 patients treated with MMC for corneal conjunctival intraepithelial neoplasia, 2 developed contact dermatitis (testing details were not reported).⁸⁰

Antioxidant

A single report described sensitivity to pirfenoxone, an antioxidant used in Japan for the treatment of cataracts. Patch testing showed positive reactions to the eye drops and pure pirfenoxone (1% aq).⁸¹

Mucolytic

N-acetylcysteine, a mucolytic used in tear replacement eye drops, was the causative agent in a patient who developed ACD. Patch testing was positive to the preservative-free *N*-acetylcysteine eye drops (10% aq).¹²

Anesthetics

Allergic contact dermatitis to topical anesthetics is well described in the dermatology literature.⁸² These agents are available as eye drops, gels, and ointments. Reactions to anesthetics belonging to the ester group (eg, proparacaine, tetracaine) are most common. Benzocaine (5% pet) is often used as a marker for this group in patch testing. Dannaker et al⁸³ reported a patient with periorbital dermatitis allergic to both proparacaine and tetracaine, confirmed with patch testing. Cross-reactivity patterns among structural groups are not consistent.^{82,84}

Importantly, ophthalmologists and their staff are also at risk for developing occupational ACD to topical anesthetics, most often presenting as fingertip dermatitis. Liesegang and Perniciaro⁸⁵

described an ophthalmologist with a 3-year history of fingertip fissuring. Patch testing revealed a mild reaction to caine mix (lidocaine, tetracaine, and dibucaine) and severe reactions to 2 preparations of proparacaine. The reaction to proparacaine was relevant as the clinician came into contact with this topical anesthetic during slit-lamp examinations and when separating patients' eyelids for indirect ophthalmoscopy.⁸⁵ Similarly, Dannaker et al⁸³ described an ophthalmologist with chronic fingertip dermatitis, sensitized to topical proparacaine and tetracaine, confirmed with patch testing. A case by Riddell et al⁸⁶ described ACD to proxymetacaine (proparacaine) in an ophthalmologist whose affected finger was used to hold down the lower eyelid while applying eye drops.

Corticosteroids

Despite their anti-inflammatory effects and use in treatment of allergy, ACD to topical corticosteroid agents is not uncommon. Corticosteroid sensitivity should be suspected among those who fail to improve or worsen with corticosteroid treatment. Furthermore, hand-to-eye transfer is common after application of corticosteroids elsewhere.⁸⁷ Lyon and Beck⁸⁷ reported 3 patients with ACD confirmed by patch testing to topical corticosteroids (betamethasone valerate, tixocortol-21-pivalate, and hydrocortisone butyrate) used for the treatment of periorbital dermatitis. Baek et al⁸⁸ described sensitivity to topical corticosteroid agents in 18 of 315 patch-tested patients; all had used these agents periorbitally. Reactions were most common to hydrocortisone.⁸⁸ Allergy to corticosteroids was originally classified on the basis of chemical structure into 5 groups but was recently reclassified into 3 groups.⁸⁹ Patch testing is also useful in identifying nonreactive corticosteroids.

RESPONSIBLE ALLERGENS: INACTIVE INGREDIENTS

Benzalkonium Chloride

Benzalkonium chloride, a quaternary ammonium compound widely used as a preservative in ophthalmic preparations, is a known sensitizer. Among a cohort of 266 patients with periorbital dermatitis patch tested to benzalkonium chloride, only 2 (0.8%) were sensitized.¹⁵ Similarly, 41 (0.9%) of 4422 patients who underwent skin patch testing to an ophthalmic panel demonstrated sensitivity to this preservative.⁹⁰ This antigen is known to cause irritant reactions on skin patch testing; therefore, doubtful or mild positive reactions should be interpreted with caution.^{90,91}

Thimerosal

Thimerosal (sodium ethyl mercuric thiosalicylate) is a preservative that historically was an important sensitizer in ophthalmic eye drops and contact lens solutions. Wilson et al⁹² reported positive

patch tests results to thimerosal in 27 of 31 patients with ocular redness, irritation, and corneal changes secondary to thimerosal-preserved contact lens solutions. All 31 patients had relief of symptoms after switching to preservative-free saline. Similarly, Tosti and Tosti⁹³ described 36 patients with thimerosal-induced allergic contact conjunctivitis. All 36 patients demonstrated positive reactions to thimerosal on skin patch testing. The high prevalence of sensitization has been explained by the presence in vaccinations. The American Contact Dermatitis Society named thimerosal as a “non-allergen of the year” to highlight its lack of clinical relevance despite high positivity rates.⁹⁴ Despite the US Centers for Disease Control and Prevention recommendation for removal,⁶ this preservative is still used in vaccinations.

Phenylmercuric Acetate/Nitrate

The use of phenylmercuric acetates or nitrates in eye drops has declined with replacement by other non-mercury-containing preservatives.⁹⁵ However, phenylmercuric acetate is present in fluorometholone ophthalmic ointment and remains a potential sensitizer. Landeck et al⁵ reported sensitization rates among a cohort tested to ophthalmics of 2.8% to 11.4%.

Sodium Metabisulfite

Sodium metabisulfite is a commonly used preservative in ophthalmics and other topical medications including anesthetic preparations, corticosteroids, and antifungal creams.⁹⁶ Sensitization to this preservative remains rare. A single case by Seitz et al⁹⁶ described ACD to sodium metabisulfite, present in levobunolol eye drops.

Polyaminopropyl Biguanide

Polyaminopropyl biguanide is a preservative that may be found in contact lens solutions. Sensitivity seems to be low⁹⁷; however, clinicians should be aware of this potential allergen.^{98–100}

Chlorobutanol

Chlorobutanol is an alcohol with an ability to cross the bacterial lipid layer.⁹¹ A single report by García-Medina et al¹⁰¹ described presumed ACD to chlorobutanol through elimination and a positive conjunctival provocation test; patch testing was negative.

RESPONSIBLE ALLERGENS: CONTACT LENSES

In addition to sensitivity to preservatives in contact lens solutions, ACD to the constituents of lenses has been reported. Among a cohort of 20 patients with “contact lens intolerance,” 2 patients reacted to hydroxyethyl methacrylate and triethylene glycol diacrylate, the main components of soft contact lenses.¹⁰²

RESPONSIBLE ALLERGENS: NON-OPHTHALMICS

Periorbital ACD may be caused by numerous agents other than ophthalmics (Table 3), including cosmetics, skin care products,

shampoos, and hair dyes.⁵ Allergic contact dermatitis to ingredients in baby shampoo, used to treat blepharitis, has been reported.¹⁰³ Further, transfer of allergens from the hands (“ec-topic” allergy) is well described. Acrylates from artificial nails and gold often present in this way. Finally, “airborne” allergy via aerosolized particles typically presents solely on exposed skin, especially the eyelids.

FALSE-NEGATIVE PATCH TESTING

A relatively high false-negative rate in patch testing ophthalmic agents has been reported. There are different proposed hypotheses to explain this phenomenon. First, the relatively thin epidermis of the eyelid may facilitate increased antigen penetration compared with the back or arm, sites commonly used for skin patch testing. Second, the low concentration of hapten in commercial products may not be sufficient to elicit response on traditional patch testing when solely testing the product itself. Because ophthalmic medications are often liquids, evaporation before patch placement may occur.⁴⁵ Finally, Silvestre et al⁴⁶ hypothesized that irritants in eye drops (eg, benzalkonium chloride) may facilitate enhanced penetration of allergens. Patch-testing clinicians have reported several successful adjuvant methods for testing ophthalmic agents for presumed ACD (Table 4).

TABLE 3. Non-Ophthalmic Causes of Periorbital ACD

Mode of Exposure	Potential Sources: Examples of Common Allergens
Direct Application/ contact	Makeup, moisturizers, anti-aging products: emulsifiers, preservatives, carmine, shellac in mascara False eyelash adhesives: acrylates, colophony Makeup remover: emulsifiers, preservatives, surfactants Lid soaks/cleansers: emulsifiers, preservatives, surfactants Wipes: preservatives, fragrances Hair products: emulsifiers, preservatives, surfactants Hair dye: paraphenylenediamine Sunscreen: chemical or physical blockers, preservatives, fragrances Eyelash curler: nickel, rubber Glasses: nickel Tweezers: nickel Makeup applicators/sponges: nickel, rubber Goggles: rubber
Ectopic/transfer	Jewelry: gold Artificial, acrylic, gel, and shellac nails: acrylates Nail polish: toluene sulfonamide resin
Airborne	Fragrances Plants: sesquiterpene lactones
Connubial	Partner's products

TABLE 4. Alternative Testing Methods for ACD to Ophthalmics

Method: Description	Reference: Hapten	No. Patients	Results Using Alternative Method	Results Using Standard Method: Testing "As Is" Under Chamber
Scarification or scratch patch test: gentle abrasion of skin in crisscross pattern using lancet before patch placement	Thomas et al ¹⁰⁴ ; phenylephrine	1	2+ D3 to pure phenylephrine 10% aq and eye drops containing 5% phenylephrine	Not done
	Erdmann et al ¹⁰⁵ ; levobunolol	1	2+ D7 to pure levobunolol 0.5%–2% aq and 0.5%–2% pet	Not done
	Akita et al ¹⁰⁶ ; phenylephrine	1	2+ D7 to pure phenylephrine 2% and 5% pet and eye drops containing 5% phenylephrine	Negative
	Linares Mata et al ³⁴ ; dorzolamide	2	2+ D4 to pure dorzolamide 5% aq and pet in both patients	Negative
	Gonzalo-Garijo et al ²⁰ ; carteolol	1	Negative	Negative
	Yamamoto et al ¹¹ ; EAA	1	1+ D3 to eye drops containing EAA 0.1% and pure EAA 0.2% aq	Negative to eye drops containing EAA, 1+ D3 to pure EAA 0.2% aq
	Okereke and Cohen ⁹ ; alcaftadine	1	3+ (day unknown) to 0.25% alcaftadine ophthalmic solution	1+ reaction (day unknown) to 0.25% alcaftadine ophthalmic solution
	Wilkinson ¹⁰⁷ ; levobunolol	1	1+ D6 to preservative-free eye drops	Negative
	Koch ¹⁰⁸ ; timolol, levobunolol, pilocarpine	3	containing levobunolol 0.5% Patients 1 and 2: 1+ D3 to pure timolol 1% aq and 2+ D3 to eye drops containing timolol Patient 3: 1+ D3 to pure levobunolol 1% aq, 2+ D3 to eye drops containing levobunolol, and 1+ D3 to eye drops containing pilocarpine	Negative (only used this method for testing pure β -blockers)
	Shimada et al ³¹ ; dorzolamide	1	2+ D3 to pure dorzolamide 5% and 10% aq and 10% pet. Negative to eye drops containing dorzolamide	Negative
Skin prick: pricking the skin with prick-test lancet (~10×) before patch placement Stripped skin: adhesive tape applied and removed ~10× to 20× to remove horny layer of skin before patch placement	Delaney et al ²⁹ ; dorzolamide	3	Negative D5 to pure dorzolamide 5% (vehicle unknown)	Negative
	Akita et al ¹⁰⁶ ; phenylephrine	1	Doubtful D7 to eye drops containing 5% phenylephrine	Negative
	Linares Mata et al ³⁴ ; dorzolamide	2	Negative	Negative

ROAT: daily application of a pea-size amount of the eye drop to the same area on patient's skin (typically volar forearm) tested open for 1 to 2 wk	Cusano et al ⁴⁷ ; pilocarpine	1	Positive (erythema, vesicles) after twice daily application on D10 to eye drops containing pilocarpine. Repeat ROAT with pilocarpine eye drops containing different vehicle, again positive.	Negative
	Camarasa et al ⁵⁷ ; sodium cromoglycate	1	Positive (severe, vesicular eczema) D4 after twice daily application of eye drops containing sodium cromoglycate	Negative
	Jerstad and Warshaw ²⁶ ; latanoprost	1	Strong positive reaction D4 to eye drops containing latanoprost	2+ D4 to eye drops containing 0.005% latanoprost, negative to vehicle
	Kalavala and Statham ³⁵ ; timolol, dorzolamide	1	Negative (2 wk)	Negative
	Kluger et al ³⁶ ; dorzolamide	1	Positive D3 to eye drops containing dorzolamide + timolol; repeat testing positive D2 to eye drops containing dorzolamide alone	Negative
	Gonzalo-Garjón et al ²⁰ ; carteolol	1	Negative	Negative
	Camarasa et al ⁵⁷ ; sodium cromoglycate	1	2+ reaction D4 to sodium cromoglycate 1% pet + benzalkonium 0.1% pet	Negative to pure sodium cromoglycate 1% pet and pure benzalkonium chloride 0.1% pet
	Silvestre et al ⁴⁶ ; apraclonidine	1	2+ D4 to pure apraclonidine 10% aq (1% negative) and 2+ D4 to eye drops containing 0.5% apraclonidine	Negative to lower concentrations
	Kalavala and Statham ³⁵ ; timolol, dorzolamide	1	2+ D4 to pure timolol 10% pet (5% negative) and pure dorzolamide 40% pet (20% negative)	Negative to lower concentrations
	Pigatto et al ⁷⁷ ; β -interferon	1	Negative patch test with inhibited preparation.	2+ D3 to eye drops containing β -interferon tested as is and diluted 1:2

(Continued on next page)

TABLE 4. (Continued)

Method: Description	Reference: Hapten	No. Patients	Results Using Alternative Method	Results Using Standard Method: Testing "As Is" Under Chamber
Lymphocyte proliferation assay: peripheral blood mononuclear cells isolated and resuspended in enriched culture medium + hapten or control. Thymidine added D3. Incorporated radioactivity determined via scintillation counting and compared with controls	Thomas et al ¹⁰⁴ ; phenylephrine	1	Patient's cells showed "enhanced specific proliferation" on stimulation with phenylephrine compared with controls	2+ D3 to phenylephrine 10% aq
Prick test: diluted pure hapten injected into epidermis using prick-test lancet	O'Donnel and Foulds ²² ; timolol	1	2+ reaction D4 to pure timolol 0.5% (vehicle unknown)	Negative D7 to pure timolol 0.5% (vehicle unknown)
	Thomas et al ¹⁰⁴ ; phenylephrine	1	"Eczematous reaction" D2 to eye drops containing 5% phenylephrine	2+ D3 to phenylephrine 10% aq
	Delaney et al ²⁹ ; dorzolamide	6	Negative D2 to eye drops containing dorzolamide	Negative
	Kluger et al ³⁶ ; dorzolamide	1	Negative D3	Negative
	Villarreal ³⁷ ; phenylephrine	12	7/12 patients had positive response D2 (conjunctival pruritus, lacrimation, erythema, or eyelid edema)	Negative in 11/12 patients. 1 patient had 1+ D7 to pure phenylephrine 1% pet
Provocation test or conjunctival challenge: application of eye drop directly to conjunctiva, can be performed using serial dilutions of pure ingredient	Delaney et al ²⁹ ; dorzolamide	2	Recurrence of eyelid dermatitis within 2 d of recommencing eye drops containing dorzolamide	Negative
	Linares Mata et al ³⁴ ; dorzolamide	2	Positive with application of eye drops containing dorzolamide in both patients	Negative
	Lai et al ¹⁰⁹ ; latanoprost	2	Recurrence of eyelid dermatitis within days of recommencing eye drops containing latanoprost	Not done
	Perez-Rodriguez 2008 ²⁷ ; levobunolol and latanoprost	1	Recurrence of eyelid dermatitis within 2–3 d of separate reintroduction of levobunolol and latanoprost	Positive (strength of reaction unknown) D4 to levobunolol (concentration and vehicle unknown) and eye drops containing latanoprost 0.005%
	Gonzalo-Garjio et al ²⁰ ; carteolol	1	Positive (palpebral edema, pruritus, and periorbital and conjunctival hyperemia) within 24 h	Negative

Epidermal Manipulation

Manipulation of the epidermal barrier via scratching, pricking, or tape stripping before patch placement may enhance antigen penetration.^{9,11,20,29,31,34,104–108} Scarification or the “scratch patch test” involves abrasion of the epidermis in a crisscross pattern using a lancet before patch placement (Fig. 3A, B). Akita et al¹⁰⁶ reported a strong reaction on day 7 to pure phenylephrine 2% and 5% pet and eye drops containing 5% phenylephrine on scarified skin, whereas patch placement on normal skin was negative. Similarly, Linares Mata et al³⁴ reported 2 separate patients with strong reactions on day 4 to pure dorzolamide 5% aq on scarified skin, but no reaction on normal and tape-stripped skin. Wilkinson¹⁰⁷ used a modified method by pricking the skin with a prick-test lancet before patch placement. This resulted in a mild reaction on day 6 to preservative-free eye drops containing levobunolol 0.5%; traditional patch testing was negative.¹⁰⁷

“Tape stripping” (repeated application of adhesive tape) before patch placement has been used to remove the horny layer of the skin and enhance antigen penetration (Fig. 3C). Koch¹⁰⁸ reported 3 patients with positive reactions to pure β -blockers including timolol and levobunolol on tape-stripped skin. All 3 were negative to the same concentration of β -blockers tested on normal skin.¹⁰⁸ Shimada et al³¹ elicited positive reactions using a similar tape stripping method to pure dorzolamide; standard patch testing was negative.

Importantly, epidermal manipulation may result in irritant patch test reactions. Because these methods have not been well validated or standardized, we recommend identical testing on healthy controls to help differentiate allergic versus irritant reactions.

Repeat Open Application Test

The ROAT of ophthalmic agents is well described.^{20,26,35,36,47,57} This involves application of a pea size amount of the ophthalmic medication to the same spot on the patient's arm (typically the forearm or antecubital fossa) twice daily for 1 to 2 weeks. A pruritic, papular, and/or vesicular rash in this area signifies a positive reaction (Fig. 4A, B). One of the earliest reports of this method was by Cusano et al⁴⁷ in 1993. The patient developed erythema and vesicles after twice-daily applications of eye drops containing pilocarpine on day 10. A second ROAT with pilocarpine eye drops containing a different vehicle was again positive, whereas traditional patch testing to the eye drops was negative. Camarasa et al, Jerstad and Warshaw, and Kluger et al reported similar results using ROAT to cromoglycate, latanoprost, and dorzolamide, respectively.^{26,36,57}

Compound Allergy

As mentioned above, Silvestre et al⁴⁶ postulated that irritants such as benzalkonium chloride in eye drops may enhance penetration and subsequent sensitization of other antigens. An interesting case by Camarasa et al⁵⁷ described a strong reaction on day 4 to a

sodium cromoglycate 1% pet + benzalkonium 0.1% pet mixture, after positive ROAT with the eye drops. Importantly, the patient was negative on patch testing to the individual constituents (pure sodium cromoglycate 1% pet and pure benzalkonium chloride 0.1% pet). This group proposed that benzalkonium chloride, an irritant, facilitated easier penetration of cromoglycate.

Increase Concentration

As with all purified antigens used in patch testing, it is important to find a concentration that will elicit a reaction yet is nonirritating and nonsensitizing. Increasing the testing concentration of the purified ophthalmic agent may be necessary to elicit a positive patch test result.^{35,46} Silvestre et al⁴⁶ reported a strong reaction on day 4 to pure apraclonidine 10% aq; 0.25%, 0.5%, and 1% were negative. The patient also had a strong reaction to his eye drops containing apraclonidine at 0.5%. Apraclonidine 10% aq was negative on patch testing of 20 healthy controls. Similarly, Kalavala and Statham³⁵ observed positive reactions only at higher testing concentrations of timolol 10% pet (5% was negative) and dorzolamide 40% pet (20% was negative); ROATs were also negative. These higher concentrations were negative on patch testing 10 controls.³⁵ De Groot recommends testing concentrations of 0.5% pet for timolol and 5% pet for dorzolamide, both of which would not have been high enough to elicit a reaction in this patient.¹³

Antibody Test

A single report by Pigatto et al⁷⁷ described use of an antibody against an ophthalmic active ingredient. The patient initially had a strong reaction to his β -interferon containing eye drops. The individual inactive ingredients in the eye drops were all negative on further patch testing, although purified β -interferon was not



Figure 3. A and B, Clinical photographs depicting the scarification or scratch patch test method (A), with a positive result (B). C, Clinical photograph depicting the tape stripping method.



Figure 4. A and B, Clinical photographs of 2 different patients depicting positive ROATs.

available. Therefore, the authors used an antibody to inhibit the active ingredient in the eye drops (anti- β -interferon), which resulted in a negative patch test result.

Lymphocytic Proliferation Assay

The lymphocyte proliferation assay or lymphocyte transformation test is a controversial method for detecting delayed-type hypersensitivity. This test involves culturing peripheral lymphocytes with hapten and thymidine. Proliferation of lymphocytes in the presence of the hapten signifies a “positive” result or delayed-type hypersensitivity, although this has not been well validated or proven reproducible and is commonly associated with false-positive results.^{110,111} Thomas et al¹⁰⁴ described a patient with a positive lymphocyte proliferation assay and patch test result (strong reaction at day 3) to purified phenylephrine, the active ingredient in his eye drops.

Prick Test

Prick tests are typically used in detection of type I or immediate sensitization including urticaria or anaphylaxis by injection of a diluted pure hapten into the epidermis using a prick-test lancet. However, this method has been used to detect delayed-type hypersensitivity to ophthalmic agents. O'Donnell and Foulds²² described a strong reaction on day 4 to pure timolol 0.5% on prick testing; patch testing using the same concentration was negative. Thomas et al¹⁰⁴ reported development of an eczematous reaction on day 2 after prick testing using the patient's phenylephrine eye drops. Patch testing showed a strong reaction on day 3 to purified phenylephrine 10% aq.

Provocation Test

A provocation test or conjunctival challenge is typically done in presumed cases of ACD to ophthalmic agents after negative patch testing and/or trial of alternative testing methods. The provocation

test involves application of the eye drop or serial dilutions of the purified ingredient directly to the conjunctiva. Recurrence of eyelid dermatitis and pruritus is indicative of a positive result. A case series by Villarreal³⁷ described 11 of 12 patients with a positive conjunctival challenge by day 2 after application of eye drops containing phenylephrine. Patch testing to pure phenylephrine 1% pet was only positive in 1 patient. Delaney et al²⁹ reported a positive provocation test with recurrence of eyelid dermatitis within 2 days of recommencing eye drops containing dorzolamide. Standard patch testing, scratch patch testing, and prick testing were negative to eye drops and pure dorzolamide 5%. Several other patch testing clinicians reported similar findings with varied ophthalmic agents.^{20,27,34,109}

MANAGEMENT

The most important factor in the management of eyelid ACD is identification and avoidance of the causative agent. As the availability and use of single-dose, preservative-free eye drops increase, preservative allergy is easier to manage. In addition to elimination of allergens, patients should be counseled on avoidance of common irritants including anti-aging products and harsh facial cleansers.

SUMMARY

Allergic contact dermatitis to ophthalmic medications is common and includes both active and inactive ingredients. A challenge to diagnosis includes the high frequency of false-negative patch test results. There are several additional testing methods reported in the literature with varied success in eliciting positive reactions. More studies are needed to evaluate the appropriate concentrations and vehicles for testing newer medications and standardizing unconventional patch testing methods.

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