Oral Azithromycin for the Treatment of Meibomitis

Common treatment regimens for meibomitis include eyelid hygiene, lubricants, topical antibiotics, topical steroids, and systemic medications. Azithromycin is a macrolide antibiotic with robust antimicrobial and anti-inflammatory properties, and topical azithromycin, in a 0.1% ophthalmic solution (Azasite) has been shown to be efficacious in treating anterior and posterior blepharitis. Azithromycin's pharmacokinetic profile adds to its potential value in treating meibomitis: a single 1 g oral dose results in high conjunctival tissue and tear fluid concentrations that persist for at least 14 days. Pulsed oral azithromycin has been reported to improve ocular signs and symptoms in patients with papulopustular rosacea. Based on this, azithromycin has potential efficacy in treating meibomitis using a short, pulsed dosing regimen, and we have used azithromycin in this fashion for the treatment of symptomatic meibomitis. We performed a retrospective review of patients receiving oral azithromycin for meibomitis to determine its impact on relieving patients' symptoms.

Methods | The medical records of all patients seen in one author's (T.P.M.) clinic at the Francis I. Proctor Foundation between January 1, 2009, and December 31, 2010, and who were treated with oral azithromycin for symptomatic meibomitis were reviewed. Patients were excluded if they had unrelated ocular pathology likely contributing to symptoms or if no follow-up had been recorded at the time of review. Collected data included patient demographic characteristics, all recorded prior (failed) treatments, and all concurrent treatments used in combination with oral azithromycin. Azithromycin was dosed as 1 g orally once per week for 3 weeks. Time to follow-up, subjective improvement, and adverse events as seen on examination or per patient report were recorded.

Results | Thirty-two patients (19 female; mean age, 60 years) with meibomitis qualified for this study based on inclusion and exclusion criteria. All patients reported poor response to commonly prescribed treatments including topical antibiotics and steroids (Table), and all patients were treated with oral azithromycin as well as concurrent topical corticosteroid treatment for the duration of the study period, most frequently with sulfacetamide sodium, 10% prednisolone acetate, 0.25%, drops applied twice daily to the eyelids. Other concurrent treatments included warm compresses (13 patients [41%]), topical metronidazole (6 patients [19%]), and topical antibiotics (3 patients [9%]).

<table>
<thead>
<tr>
<th>Table: Symptomatic Improvement Based on Prior Treatments</th>
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<tr>
<td>Intervention</td>
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<tr>
<td>Azithromycin, topical steroid, and any other concurrent treatment</td>
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<td>Azithromycin and topical steroid only</td>
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Twenty-four patients (75%) reported symptomatic improvement with their treatment regimen at their follow-up visit (mean time to follow-up, 5.6 weeks, range, 3-11 weeks). Of patients with previous failure of steroids, other antibiotics, or both, similar rates of symptomatic improvement were seen (Table). When analyzing patients who were treated solely with oral azithromycin and topical steroid without any other concurrent treatments, 8 (67%) reported symptomatic improvement, including 7 (64%) of those who had previous failure of topical steroid treatment (Table). The most commonly reported adverse effects included gastrointestinal upset (3 patients [9%]) and ocular discomfort (2 patients [6%]), none of which required discontinuing use of azithromycin.

Discussion | The results of our study support oral azithromycin as being efficacious in treating symptomatic meibomitis, particularly in patients who have had failure of other commonly prescribed interventions. All of our patients had a history of failure of other treatments, but 75% reported symptomatic improvement with a regimen including oral azithromycin. While all patients also received a topical steroid, similar numbers noted improvement even when controlling for those who had past failure of steroid treatment. Adverse effects were minimal and mild, supporting the safety of this intervention. Our results further support the results of a recent small prospective study of 13 patients receiving pulsed oral azithromycin for treatment of non-rosacea posterior blepharitis, which showed similar improvement in patients' symptoms and clinical signs. Based on our study as well as the limited evidence in the current literature, oral azithromycin appears to be a valuable tool in the treatment of meibomitis and further prospective studies would be justified to better assess efficacy and duration of effect.

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**Ocular Demodicosis as a Potential Cause of Pediatric Blepharoconjunctivitis**

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**Purpose:** To report *Demodex* infestation in pediatric blepharoconjunctivitis.

**Methods:** A retrospective review of 12 patients, with ages from 2.5–11 years, with chronic blepharoconjunctivitis who failed to respond to conventional treatments. *Demodex* was detected by lash sampling and microscopic examination. Patients were treated with 50% tea tree oil (TTO) eyelid scrubs or 5% TTO ointment eyelid massages for 4–6 weeks.

**Results:** *Demodex* mites were found in all, but 1 case had cylindrical dandruff in the lashes. After 1 week of TTO treatment, all patients showed dramatic resolution of ocular irritation and inflammation while *Demodex* counts dropped. All corneal signs resolved within 2 weeks except for a residual anterior stromal scar in 1 eye. During a follow-up period of 8.3 ± 4.6 months, 1 patient showed recurrent inflammation, which was successfully managed by a second round of TTO treatment.

**Conclusions:** Demodicosis should be considered as a potential cause of pediatric refractory blepharoconjunctivitis. Eyelid scrubs or massage with TTO could be an effective treatment regimen in these cases.

**Key Words:** blepharoconjunctivitis, *Demodex*, pediatric, tea tree oil

*Cornea* 2010;29:1386–1391

Blepharoconjunctivitis is a common eye disease in the pediatric population, which, in severe cases, may involve the cornea, resulting in visual impairment. Few details are known about its underlying etiology in part because children are less cooperative with eyelid swabs for microbial work-ups.1–5 *Staphylococcus* has been found in 7%–52% of pediatric cases,11–3 a rate much lower than the 80% incidence in adults.6

The common therapeutic regimen includes eyelid hygiene, topical steroids/antibiotics, and systemic erythromycin or doxycycline.14,7 Despite treatments that may last months or years, the reported recurrence rate remains considerably high, ranging from 40%6,9 to 56%,3 although some cases become refractory.3–5 These intriguing findings prompted us to speculate that there might be other causes for pediatric blepharoconjunctivitis.

Recently, our clinical experience revealed that successful treatment of ocular demodicosis resolves blepharoconjunctivitis in adults when traditional therapies have failed.8,9 Ocular demodicosis is caused by *Demodex* mites burrowing in the eyelash follicles and meibomian glands.10 For adults, common clinical manifestations of ocular demodicosis include blepharitis with lashes carrying cylindrical dandruff (CD),11 meibomian gland dysfunction with abnormal lipid film, and intermittent trichiasis.8 Some cases may present with keratitis manifested by superficial corneal vascularization, marginal infiltration, phlyctenular lesion, superficial opacity, and/or nodular scarring.9 It is generally believed that ocular *Demodex* infestation is common in adults, but rare in children.12–14

Furthermore, most pediatric dermatological demodicosis develops when immunity is compromised by administration of steroids,13 other immunosuppressive agents,15,16 leukemia, or human immunodeficiency virus.17,18 It is no wonder that most physicians do not consider ocular demodicosis as a cause of blepharoconjunctivitis in healthy pediatric patients.

Herein, we report ocular demodicosis in 12 healthy pediatric patients with a history of recurrent blepharoconjunctivitis, which failed to respond to traditional treatments. Using a recently reported regimen consisting of eyelid scrub with 50% tea tree oil (TTO)8,9 or eyelid massage with 5% TTO ointment, the blepharoconjunctivitis was resolved in a short period. The clinical significance of these findings is further discussed regarding the pathogenesis of pediatric blepharoconjunctivitis.

**MATERIALS AND METHODS**

This study was approved by the ethics committee of Ocular Surface Research & Education Foundation (Miami, FL; †State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China; ‡Steve G. Safran MD Clinics, Lawrenceville, NJ; §Department of Ophthalmology, The Second Affiliated Hospital, Fujian Medical University, Quanzhou, Fujian, China; and ¶Research Institute of Ophthalmology, Cairo, Egypt.

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Dr. S. C. G. Tseng and Dr. Y. Gao have filed 2 patents for the use of tea tree oil and its ingredients for treating demodicosis. No other authors have any proprietary interest in any material mentioned in this study.

This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Eye Institute or the National Institutes of Health.

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FL) to retrospectively review the medical records of 12 patients (24 eyes) who were proven to have ocular demodicosis and were seen at Ocular Surface Center, Miami, FL (2 cases), the practice clinic of Steve Safran MD (4 cases), and the Department of Ophthalmology, The Second Affiliated Hospital, Fujian Medical University, China (6 cases) (Table 1). Ocular demodicosis was confirmed in cooperative patients (10 patients) by microscopic examination of epilated lashes as previously reported.\textsuperscript{11,24} Briefly, 2 lashes with CD were epilated from each eyelid under slit lamp and mounted on glass slides. One drop of saline or fluorescein solution was applied to dissolve the CD and to allow embedded \textit{Demodex} to migrate out. The total \textit{Demodex} counts were determined under a light microscope. For noncooperative patients, epilation was carried out under general anesthesia (1 patient) and 2–4 lashes were removed from each eyelid for more thorough assessment. One patient refused epilation, and therefore, the diagnosis was made by the presence of CD on the root of lashes, a reliable diagnostic sign as previously reported.\textsuperscript{11} Six patients received eyelid scrubs with 50% TTO 3 times weekly for 4–6 weeks similar to what has been reported.\textsuperscript{8,9,25} In brief, a cotton tip wetted in 50% TTO was used to scrub the lash roots from one end to the other. A total of 6 strokes were applied to each eyelid. A dry cotton tip was used to remove excess TTO and loosened CD from the eyelid margin 5 minutes later. This procedure was repeated for a total of 3 times with 5 minutes of rest between each repetition. The other 6 patients, who were not cooperative to the TTO eyelid scrub, received eyelid massage with 5% TTO ointment twice a day for 4–6 weeks as follows. After washing the face and eyelids with baby shampoo or soap and rinsing with warm water, a small amount of 5% TTO ointment was smeared onto both index fingers. With the eyes closed, the eyelid margins were massaged from one end to the other, for 5 minutes, leaving the ointment without washing. \textit{Demodex} counts were repeated after 4–6 weeks treatment in 4 patients in which a second epilation was amenable. The medical records, including the history of present illness, results of complete eye

<table>
<thead>
<tr>
<th>Number</th>
<th>Age (Yr)/Sex</th>
<th>Symptoms</th>
<th>Lashes and Eyelid Margin</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CD</td>
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<tr>
<td></td>
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<td>Malaligned Lashes</td>
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<tr>
<td>1</td>
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<td>Sporadic</td>
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<tr>
<td>2</td>
<td>5/M</td>
<td>Recurrent chalazia</td>
<td>Sporadic</td>
</tr>
<tr>
<td>3</td>
<td>6/F</td>
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</tr>
<tr>
<td>4</td>
<td>6/M</td>
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</tr>
<tr>
<td>5</td>
<td>7/F</td>
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</tr>
<tr>
<td>6</td>
<td>7/M</td>
<td>Recurrent chalazia, FBS</td>
<td>Diffuse</td>
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<tr>
<td>7</td>
<td>8/F</td>
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</tr>
<tr>
<td>8</td>
<td>8/F</td>
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</tr>
<tr>
<td>9</td>
<td>9/F</td>
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<td>Sporadic</td>
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<tr>
<td>10</td>
<td>10/F</td>
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</tr>
<tr>
<td>11</td>
<td>11/F</td>
<td>Itching, redness, pain, burning blurred vision</td>
<td>Sporadic</td>
</tr>
<tr>
<td>12</td>
<td>11/M</td>
<td>Itching, LS, tearing, blurred vision</td>
<td>–</td>
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</tbody>
</table>

All the symptoms and signs involved both eyes except for those specifically mentioned.

\textsuperscript{*, yes; –, no; FBS, foreign body sensation; LS, light sensitivity; MGD, meibomian gland dysfunction; NA, not available; UCVA, uncorrected visual acuity.}
examination, and external photographs were reviewed and compared from the first to the last visits regarding changes in symptoms and signs.

RESULTS

These 12 patients included 7 women and 5 men, with ages from 2.5 to 11 years. Demographic and other clinical features are summarized in Table 1. Their symptoms included redness (18 eyes in 9 patients), itching (16 eyes in 8 patients), pain (10 eyes in 5 patients), blurred vision (9 eyes in 5 patients), light sensitivity (8 eyes in 4 patients), foreign body sensation (8 eyes in 4 patients), recurrent multiple chalazia (8 eyes in 4 patients), and tearing (4 eyes in 2 patients) lasting for 2 months to 3 years. Before referral, they were all diagnosed as blepharoconjunctivitis. In addition, allergic conjunctivitis was also suspected in 4 patients and keratitis was noted in another 4 patients. These symptoms persisted despite prior treatments including topical antibiotics (12 patients), topical steroids (11 patients), topical antiallergy eyedrops (4 patients), eyelid scrub using baby shampoo (4 patients), oral erythromycin (2 patients), and tetracycline (1 patient) for 2 months to 1 year.

One patient had a prior history of ocular rosacea. There was no history of notable systemic disorders except for hay fever in 1 patient (case 10) and allergy to dust mites in another (case 3).

At presentation, 10 of 12 patients had CD in their lashes, which was sporadic in 9 patients and diffuse in 1 patient (Fig. 1A). The other 2 patients did not show obvious CD at the lashes. Microscopic examination revealed Demodex mites in all 11 patients in which epilation was amenable (Table 1), including the 2 patients that did not show CD. Demodex follicularum was found in 10 patients and Demodex brevis in one (case 1). The Demodex counts are listed in Table 1. Lashes were maldirected in 8 eyes of 4 patients, although not to the extent of trichiasis. Severe eyelid margin swelling was also noted in 2 eyes (Fig. 1B). Ten patients had bilateral meibomian gland dysfunction defined by plugging of the orifice or poor expression of the meibum on digital expression. Four patients also presented bilateral multiple chalazia with 2–6 recurrences. All patients had notable conjunctivitis as evidenced by redness involving bulbar conjunctiva (Fig. 1C) and papillary follicular reaction involving bilateral upper and lower tarsal conjunctiva. In addition, corneas showed subepithelial infiltrates in 3 eyes (Fig. 1D), paracentral corneal ulcer in 2 eyes, neovascularization in 2 eyes, phlyctenular keratitis in 2 eyes, and superficial punctate keratopathy in 2 eyes (Table 1).

After eyelid scrub with TTO or eyelid massage with TTO ointment, CD disappeared from the eyelashes (Fig. 1E) with reduction of Demodex counts to 0–1 in the 4 cases in which a second epilation was amenable. Just 1 week after treatment, all patients reported subjective improvement of ocular surface irritation, followed by complete resolution of eyelid margin swelling (Fig. 1F) and conjunctival redness (Fig. 1G). Papillary follicular reaction and all corneal lesions including ulcer, punctate keratopathy, and infiltration were gone within 2 weeks (Fig. 1H). A localized anterior stromal scar remained in 1 eye (case 10) that initially presented with scattered subepithelial infiltrates. Visual acuity was improved by 1 Snellen line in 3 eyes, 2 Snellen lines in 4 eyes, and 5 Snellen lines in 2 eyes. During a mean follow-up of 8.3 ± 4.6 months (range, 5–18 months), 1 patient (case 3) had 1 recurrent episode of blepharoconjunctivitis, which was successfully treated by another round of TTO treatment. Three patients with multiple recurrent chalazia were treated by bilateral chalazion incision (4 eyes of 2 patients) or intraleSIONal steroid injection (2 eyes of 1 patient), with no further recurrence during the follow-up period.

Representative Case Report (Case 1)

A 2.5-year-old boy had bilateral intermittent itching, redness, and multiple chalazia for 10 months. No improvement had been achieved after 5 months of treatment with hot compresses, eyelid scrub with baby shampoo, topical tobramycin and dexamethasone, and erythromycin ointments. On presentation, chalazia were located in the temporal upper eyelid and central lower eyelid of the right eye and in the temporal lower eyelid of the left eye with erosion in the overlying skin (Fig. 2A). Although Demodex blepharitis was suspected, microscopic examination of 8 lashes from 2 eyes epilated under general anesthesia did not reveal any mites. Intralallesion injection of triamcinolone (Bristol-Myers Squibb Company, Princeton, NJ) resulted in complete resolution of chalazia. However, multiple chalazia occurred 2 months later in new locations: the central upper eyelid and nasal lower eyelid of the right eye and nasal and temporal lower eyelid of the left eye. Repeated examination under general anesthesia showed inflammation involving the eyelid margin and palpebral and bulbar conjunctiva (Fig. 2B) and prominent follicular reaction in the fornix and palpebral conjunctiva of both eyes (Fig. 2C). The meibomian gland orifices were plugged (Fig. 2D). Both corneas were normal. In addition, both lower eyelids showed sporadic crusting (Fig. 2E), but the upper eyelids showed sporadic CD (Fig. 2F). Microscopic examination of 16 lashes from both eyes revealed one D. brevis (Fig. 2G). Eyelid margin and conjunctival swab cultures were negative for bacteria and fungi. After 1 week of TTO treatment, the patient’s symptoms were relieved completely, the lashes were clean without CD, and the conjunctival inflammation was resolved. No recurrence was noted during the follow-up period of 6 months.

DISCUSSION

Although Demodex has been implicated as a potential cause of blepharoconjunctivitis in adults, its role in children remains unclear. In this study, ocular demodicosis was diagnosed in 12 pediatric patients with blepharoconjunctivitis resistant to conventional therapy. Furthermore, TTO treatment was shown to be effective in resolving symptoms in these patients. These results suggest that demodicosis may be an overlooked cause of refractory pediatric blepharoconjunctivitis.

Diagnosis of pediatric demodicosis is challenging, if not problematic, because of their poor cooperation during examination and lash sampling. Although CD is a reliable sign for ocular demodicosis in adults, it may be less apparent in pediatric patients, as shown in 2 of our cases where Demodex mites were present without CD. Hence, the true frequency of CD in pediatric blepharoconjunctivitis is
unknown. Furthermore, the Demodex count could not be accurately assessed in children because it was difficult to epilate 2 lashes from each eyelid as is advised for adults.\textsuperscript{11} For case 1, detection of one *D. brevis* required epilation of 16 lashes under general anesthesia. Because *D. brevis* is known to burrow deep in sebaceous and meibomian glands, it may escape detection by lash sampling. Despite these limitations, we achieved microscopic detection of mites in all patients but one. In view of the fact that demodicosis is thought to be rare in the normal pediatric population,\textsuperscript{12–14} detection of a small number of mites is already of significance.

The high incidence of meibomian gland dysfunction contrasts with previous reports that meibomian gland dysfunction is mostly limited to the elderly and never found in children under 10 years.\textsuperscript{29} This may be due in part to irritation caused by *D. brevis*, which might also account for the

FIGURE 1. Photographs demonstrating ocular manifestations of pediatric Demodex infestation including CD (A), eyelid margin swelling (B), conjunctival inflammation (C), and superficial corneal infiltration (D). Eyelid scrub with TTO for 2 weeks resulted in clean lashes (E), complete resolution of eyelid margin swelling (F), conjunctival inflammation (G), and corneal infiltration (H).
high recurrence rate of chalazia in children, which is reported to be 17%–25%.30,31 Future studies are needed to determine whether multiple recurrent chalazia are caused by mite infestation and if so, whether TTO can be a more effective treatment to prevent such recurrences. Our study also found a high incidence of keratitis associated with blepharoconjunctivitis, which is well documented in adults2,32 but is infrequently reported in pediatric blepharoconjunctivitis.1,3–5 Although Staphylococcus epidermis and Staphylococcus aureus are implicated as the main pathogens in pediatric blepharoconjunctivitis,4,5 Demodex mites may serve as a vector to carry these bacteria and keep them in the eye.33 In fact, there is a strong association between the mite’s abundance and S. aureus.28,34 Future studies of comorbidity between demodicosis and microbial infection may shed light on the exact pathogenesis.

In agreement with published reports,1,3–5 topical broad-spectrum antibiotics required a prolonged course or were relatively ineffective for our patients. In contrast, eyelid scrub with 50% TTO or eyelid massage with 5% TTO ointment resulted in dramatic alleviation of symptoms and marked resolution of inflammation in the eyelid margin, conjunctiva, and cornea. This was consistent with our success in treating adult Demodex blepharoconjunctivitis using TTO.8,9,25 The 2 treatments were equally effective in eradicating mites, although we presume that they may act differently. The 50% TTO has direct killing effect on the mites, whereas the 5% may interrupt their life cycle by preventing mating.

Collectively, our results suggest that ophthalmologists should consider the possibility of demodicosis in children when presenting with blepharoconjunctivitis. Furthermore, ocular demodicosis might be present in pediatric patients during their first decade even when they are not systemically immune compromised. Further study on the pathogenic role of Demodex infestation in children with blepharoconjunctivitis might help establish the diagnostic criteria of pediatric Demodex blepharoconjunctivitis.

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