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REVIEW

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Challenges in the management of pediatric blepharokeratoconjunctivis / ocular rosacea

Moritz Claudius Daniel[a,b], Michael O'Gallagher[a], Melanie Hingorani[a], Annegret Dahlmann-Noor[a] and Stephen Tuft[a]

[a]NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Trust and UCL Institute of Ophthalmology, London, England; [b]Eye Center, University Hospital Freiburg, Freiburg, Germany

ABSTRACT

Introduction: Childhood blepharokeratoconjunctivitis is a common lid margin inflammation with secondary ocular surface disease. Its etiology is unclear and there are no randomized controlled trials to support the superiority of any treatment option.

Areas covered: We searched the following databases; Cochrane Central Register of Controlled Trials, Ovid MEDLINE and affiliated Ovid databases, EMBASE, the ISRCTN registry, Clinical- Trials.gov and the World Health Organization International Clinical Trials Registry Platform. Due to the paucity of pediatric data we also considered information from articles focused on adults.

Expert commentary: Treatment is based on the assumption that the mechanisms of BKC and rosacea keratitis are the same: meibomian gland dysfunction, bacterial colonisation of the lid margin, delayed type hypersensitivity, Demodex folliculorum, genetic predisposition and Toll-like receptors inducing release of pro-inflammatory cytokines. Generally accepted grading scales are needed. Randomized clinical trials are needed to evaluate treatment options. The effects of antibiotics, immunomodulators, osmoprotectants and essential fatty acids need further investigation.

1. Classification and epidemiology

1.1. Classification

Ocular surface disease secondary to lid margin inflammation is a common cause of ocular morbidity in children. This is now called pediatric blepharokeratoconjunctivitis (BKC), but other names have been used including ocular rosacea, phlyctenular keratitis, meibomian keratoconjunctivitis, nontuberculous keratitis, or staphylococcal blepharokeratitis. There are a range of clinical features including conjunctivitis, episcleritis, phlyctenulosis, keratitis, corneal vascularization, and corneal scarring. It is not known whether these various phenotypes reflect differences in pathogenesis and disease entity or levels of disease activity. Corneal disease in children is more likely to be severe and progress to significant vision loss even with mild lid margin inflammation than for adults. The proportion of children who subsequently progress to an adult phenotype of BKC or rosacea is unknown, but many resolve permanently before adulthood.

Chronic blepharitis is a disorder of the lid margins that can involve the anterior lid margin (lash follicles) and/or the posterior lid margin (meibomian glands). Both can lead to corneal disease. In children, posterior blepharitis is more prominent than anterior changes. Keratitis is uncommon in acute blepharitis related to styes (hordeolum externum), impetigo, herpes simplex infection, or infected meibomian cysts (acute chalazion, hordeolum internum).

1.2. Epidemiology

The age of onset of BKC is bimodal with a peak at 4–5 years [1] and a second peak in adolescence. There may be an interval of several months between the onset of symptoms and diagnosis suggesting that it is poorly recognized and probably underdiagnosed. It is not clear if males or females are more commonly affected. Some authors suggest a female predilection (48–87%) [1]. In other studies, the ratio was about 1:1 (1.6 to 1 [1], 1 to 1 [1], 1 to 1.2 [1]). The male-to-female ratio in rosacea has been reported to be 30–70% [1]. Although it has been reported that disease is more severe in South Asian and Middle-Eastern children [1], a severe phenotype has also been described in white adolescents [1]. There are no population-based studies to confirm or refute a significant association with ethnicity.

Several differential diagnoses for BKC should be considered. The most frequent cause for diagnostic confusion is chronic allergic eye disease (vernal keratoconjunctivitis, atopic keratoconjunctivitis) which differs from BKC in that there is often associated asthma or atopic dermatitis including facial and lid dermatitis, marked itch, and a significant papillary response, possibly with giant papillae in the upper tarsal conjunctiva or limbus. In some cases, atopic eye disease and BKC can coexist. Other causes for chronic ocular surface inflammation in children are rare but the presence of a molluscum contagiosum lesion close to the lid margin should be excluded. Herpes simplex keratitis should be excluded if there is unilateral disease. Phlyctenules have a reported

association with tuberculosis and very rarely with helminthiasis, leishmaniasis, and candidiasis. In areas where tuberculosis is endemic, a child with a phlyctenule should be screened for tuberculosis (e.g. Quantiferon, chest X-ray). Lash or eyebrow infestation by crab lice (*Phthirus pubis*) can cause low-grade irritation and conjunctivitis and mimic the lash crusts of anterior blepharitis, because of the possibility of sexual abuse of children with crab lice infestation of the lashes a pediatrician should be involved.

2. Methods

We searched the following databases, using the search terms 'blepharokeratoconjunctivitis,' OR 'BKC,' OR 'blepharokeratitis,' OR 'blepharoconjunctivitis,' OR 'ocular rosacea;' Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group (CEVG) Trials Register) (latest issue), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, OvidMEDLINE Daily, Ovid OLDMEDLINE (January 1946 to present), EMBASE (January 1980 to present), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), Clinical Trials.gov (www.clinicaltrials.gov), and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en) [2]. Articles written in languages other than English or German were not considered. We excluded articles which we regarded irrelevant according to the abstract. This provided 33 articles matching our criteria. We also manually collected articles mentioned in the reference lists from PubMed. Due to the lack of randomized controlled trials in this field of research, we included case reports, retrospective studies, and review articles. Information concerning the diagnosis and pathophysiology of BKC in adults was extracted because of the paucity of studies specifically addressing these topics in

children. This provided a total number of 99 results on which this review article is based.

3. Diagnosis

The diagnosis of BKC is based on a characteristic pattern of symptoms and clinical signs. The symptoms of early BKC include eye rubbing with chronically uncomfortable red eyes, photophobia, and epiphora [3–5]. There may be crusting of the lids in the morning, but discharge is not a major feature. Frequently, there is a history of recurrent chalazia. Occasionally, the disease can be relatively asymptomatic until photophobia, reduced vision, or a corneal opacity alerts the patient or parents. The disease can be markedly asymmetric or even unilateral.

3.1. Lid

Blepharitis signs include crusting with scales and collarettes at the base of the lashes (anterior blepharitis) and telangiectasia of the lid margin vessels and gaping and inspissation of the meibomian gland openings (posterior blepharitis) (Figure 1) with expression of yellow-white meibum following gentle lid pressure [6]. The lid margins may be diffusely hyperemic and thickened and there may be one or more chalazia. Chronic changes include distortion or abnormal placement of meibomian glands, loss of lashes, depigmentation of the skin, malposition of eyelashes, keratinization of the lid margin, and there can be notching of the lid margin [7]. However, in some individuals, the alteration in appearance of the lid margin and meibomian glands may be minimal.

3.2. Skin

In adults, the clinical signs of isolated blepharitis and keratitis are similar to those presenting in association with cutaneous
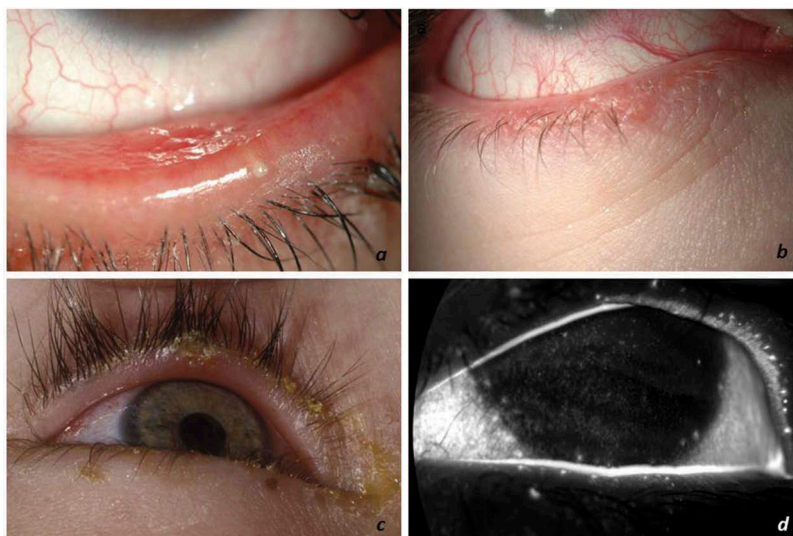

Figure 1. *a* Inspissated meibomian gland, telangiectasia, papillary changes of the palpebral conjunctiva *b* Telangiectasia, lid margin thickening and irregularity, keratinisation of the lid margin, *c* Collarettes (keratin scales and crusts encircling eyelash bases) *d* Corneal staining with fluorescein.

rosacea, and it is unclear whether there are distinctive disease mechanisms [8]. Most children with BKC do not have facial skin changes but there is an association with atopic dermatitis and acne vulgaris. In children, the association of BKC with facial rosacea is less common than in adults [9], but its prevalence is possibly underestimated [10] and acne vulgaris and rosacea should be considered if ocular symptoms associated with facial dermatosis [11]. The ophthalmologist should be able to distinguish acne vulgaris from papulopustolar rosacea. Telangiectasia and flushing are associated with rosacea, comedones are a hallmark of acne [9].

3.3. Conjunctiva

Conjunctival signs include hyperemia, micropapillae, folliculosis, mild chemosis, and the formation of phlyctenules. In severe disease, there may be an intense tarsal micropapillary response and infiltrate with a reactive ptosis and focal or diffuse limbitis. A conjunctival phlyctenule (or phlycten) is an acute inflammatory nodule most commonly seen at the limbus topped by a small white collection of polymorphonuclear leukocytes and an apical epithelial defect. Conjunctival phlycten usually resolve completely and rapidly following treatment, but there may be a characteristic triangular segment of vascularization and scarring if there has been corneal involvement. Subconjunctival crystals are not always present but may be a specific sign for this condition [12].

3.4. Meibomian glands

Meibomian gland dysfunction (MGD) causes poor tear quality and an evaporative dry eye; the tear film break-up time, the Schirmer *I* test, and tear osmolarity are abnormal in adult patients with BKC [13,14], but as these tests require a degree of patient cooperation, they are seldom used in children. In adults, the morphology of the meibomian glands is altered following chronic inflammation, which can be macroscopically visualized by meibography using transillumination of the lid

[15] or infrared imaging with computerized image analysis to estimate meibomian gland atrophy [16]. The relevance of the reported changes, e.g. gland dropout [17] in children in whom the course of disease may have been much shorter, is unknown.

3.5. Cornea

There is a spectrum of corneal changes, which can be multifocal. In mild cases, there may only be punctate epithelial lesions demonstrated with fluorescein, especially over the inferior third of the cornea, which may be secondary to evaporative dry eye or represent direct corneal involvement in BKC (Figure 2). In more severe disease, there can be corneal epithelial macrodefects, peripheral keratitis (marginal keratitis), or central keratitis with opaque corneal infiltrates sometime overlain by an epithelial defect, corneal thinning and perforation, secondary corneal vascularization, and scarring. This can lead to irregular astigmatism [18]. Each of these problems can lead to loss of vision and amblyopia, emphasizing the importance of early diagnosis and effective treatment [1].

3.6. Grading

There is no agreed classification of disease subtypes or disease activity. Different grading systems for MGD have been proposed [13]. Viswalingam et al. classified BKC based on the severity of lid and conjunctival signs as well as corneal involvement [19]. Hamada et al. graded activity and tissue damage from 0 (no inflammation of damage) to 3 (severe inflammation or damage) [20]. They considered parameters such as meibomian gland duct dilation, retro-placement of meibomian gland duct orifices, and migration of the mucocutaneous junction. In adult dry eye disease, corneal staining with grades from 0 to 5 is considered an indicator of disease activity, and Hamada et al. incorporated this into their grading system. Corneal vascularization, formation of pannus (equal to less or more
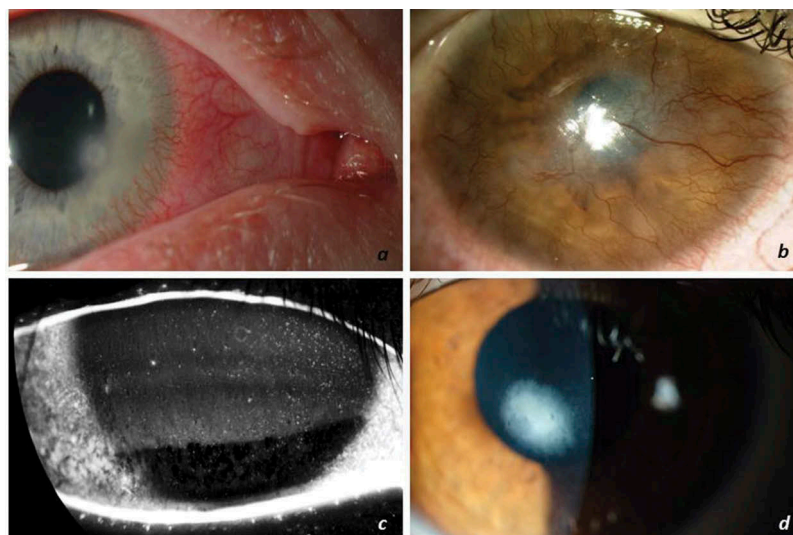

Figure 2. *a* Active keratitis with peripheral corneal vascularization *b* Central corneal vascularisation with central scarring *c* Punctate corneal epithelial defects, staining with fluorescein, and early treat film break up *d* Residual corneal scar without active inflammation.

than 3 clock hours, centripetal extension), corneal scarring, and peripheral thinning are used to grade corneal damage. However, this grading system has not been externally validated and is not in common clinical use. In practice, any system which requires detailed assessment can be difficult to perform in young children who have photophobia.

4. Pathophysiology

The proposed mechanisms that lead to BKC are principally derived from animal models and studies of rosacea, blepharokeratitis, and MGD in adults. It is assumed that the same mechanisms are active in children. It is not known whether the different clinical features of BKC are the result of different disease processes, or the result of a common pathology modified by local or environmental factors. There is broad consensus on certain key probable pathophysiological drivers in adult disease [20,21]:

- MGD: hyperkeratinization and terminal duct obstruction with qualitative and quantitative (usually hyposecretion) changes in the glandular secretion (meibum), frequently with inflammation of the meibomian glands and adjacent tissues and later atrophy of the glands (dropout). It is still unclear whether inflammation is the cause or the consequence of gland obstruction and whether the chemical changes of meibum are primary or secondary to bacterial action [22].
- Bacterial colonization of the lid margin with *Staphylococcus sp.*, *Propionibacterium acnes*, *and Corynebacteria*: bacterial lipopolysaccharides stimulate the production and release of proinflammatory cytokines such as TNF-α from the ocular surface; bacterial phospolipase A2 catalyzes the release of arachidonic acid from meibum that leads to the formation of prostaglandins and leukotrienes, while the release of free fatty acids destabilizes the tear film and promotes inflammation by neutrophil chemotaxis [23].
- Delayed type hypersensitivity response to bacterial products (e.g. *Staphylococcus aureus* protein A, ribitol teichoic acid) causing ocular surface inflammation, although other antigens may be involved [24].
- A genetic contribution is suggested by reports of a high prevalence in some ethnic groups and human leukocyte antigen associations [25]. A recent genome-wide association study identified a single-nucleotide polymorphism associated with rosacea [26].
- Dry eye disease, tear film instability, and hyperosmolarity with secondary inflammation involve pro-inflammatory cytokines and activation of several matrix metalloproteinases. Toll-like receptors 2 and 4 have been suggested to be part of the rosacea pathophysiological pathway. They respond to physical or chemical stress and can also be triggered by microbes such as *Demodex*. Upon activation, they induce the release of pro-inflammatory cytokines [27,28].
- TNF-α inhibitors (e.g. Infliximab) have successfully been used off-label in adults for the treatment of granulomatous rosacea [29]. Cytokines, chemokines, and Toll-like receptors may become potential targets for future therapeutic interventions in rosacea and possibly BKC.
- A proposed role for *Demodex* parasites is unproven in BKC [30]. Studies in rosacea have shown a focally higher density of *Demodex folliculorum* mites in the pilosebaceous units, but it is unclear whether this is cause or effect [31].

5. Treatment

Therapy targets the underlying blepharitis and specific inflammatory changes (Table 1) [21]. There are no controlled clinical trials to guide therapy [8]. Many cases of BKC require prolonged treatment and, even with all available options, for some it is difficult to achieve good inflammatory control. However, as the prognosis for resolution is good for children, the treatment aims to control the disease and minimize long-term damage until the inflammation lessens with time.

5.1. General principles of treatment in children

Treating children using drops or lid hygiene, especially small children, can be difficult. Lid hygiene may not be possible without upset in small children and if this is the case, families should be encouraged to apply what the child will tolerate, e.g. lid margin cleaning or warm compresses only. Older children (7 years and older) should be encouraged to carry out the lid hygiene by themselves, but may need supervision.

Older children should be encouraged and supported to administer eye drops themselves. Single unit vials can be used to allow children to take the drops to school without fear of 'losing the drop bottle.' The number and frequency of different medications should be minimized, within the boundaries of achieving ensuring satisfactory control, to avoid confusion and aid compliance. Treatment has to concentrate on those agents which are most likely to deliver a therapeutic result. If it is crucial to instill drops into small children to prevent serious ocular tissue damage or visual loss, parents can be taught techniques of efficient and safe restraint to allow this.

5.2. Lid hygiene

Lid hygiene is a widely accepted mechanical approach to MGD and blepharitis. Though nonstandardized and comparative evidence-based recommendations are not available (level of evidence II/III), most experts consider lid hygiene a low-cost and effective treatment [6]. It is advisable in all cases of acute or chronic lid inflammation [32]. Acute or inflamed chalazia should be treated daily with warm moist lid compresses (Figure 3). A short course of topical antibiotics can be used. Meibomian cysts tend to resolve spontaneously and in most cases in children can be safely left to do so, but they can be incised or injected locally with long-acting steroids if they do not resolve, or if they affect vision by altering lid position, although this often requires a general anesthetic in children [33]. For chronic disease, lid hygiene is usually recommended, for which there are three components: warm compresses, lid massage, and cleaning of lid debris. A warm compress helps to soften any crusts and inspissated meibum on the lid margin.

Table 1. Therapeutic options for management of pediatric blepharokeratoconjunctivis.

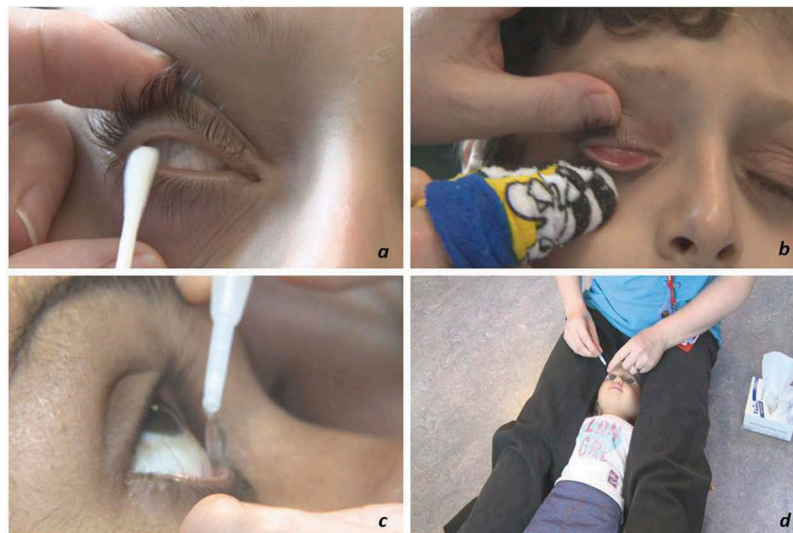| Option	Agent	Protocol
Lid hygiene		Lid margin cleaning (most important): any of these methods: cotton bud/swab soaked in water, with or without baby shampoo/bicarbonate; flannel wrapped tightly around index finger and soaked in water, with or without baby shampoo/bicarbonate; commercial lid wipes [4,6]
Topical lubricants	Hyaluronic acid 0.1%	PRN [21,42,66]
	Carmellose 0.5%	
	etc.	
Topical antihistamines/mast cell inhibitor	G Olopatadine 0.1%	BD
	G cromoglycate 2%	QDS
	G nedocromil sodium 2%	BD-QDS
	G lodoxamide 0.1%	BD-QDS
Topical antibiotic [6,21]	Oc chloramphenicol 1%	OD - BD
	Oc fusidic acid 1%	BD
	Oc erythromycin 0.5%	OD - BD
	G. moxifloxacin 0.5%	
	G. levofloxacin 0.5%	
	G. ofloxacin 0.3%	
	G azithromycin 1.5%	BD for 3 days then OD-BD for 3 days every two to four weeks
	Oc metronidazole 0.75%	Facial skin
Oral antibiotic	Erythromycin (<12 years)	250mg (or age appropriate dosage) BD for at least 6 to 12 weeks [8]
	Doxycycline (>12 years)	50-100mg OD (or weight appropriate dosage) for at least 6-12 weeks [6,21,42]
Topical ocular anti-inflammatory [6,21,42]	G fluorometholone 1%	OD-1 hourly dependent on severity
	G rimexolone 1%	
	G loteprednol 0.5%	
	G dexamethasone 0.1%	
	G ciclosporin A 0.05-2%	OD-QDS
Omega-3 oil	Flaxseed oil	2.5ml for 6 months or longer [62,63]
	Cod liver oil	Age appropriate dose
Immunosuppression	mycophenolate mofetil	Age appropriate dose [18]
	azathioprine	Supervision by pediatrician
	prednisolone	
Interventional management	Rigid contact lens	For irregular astigmatism
	Fine needle diathermy	For progressive vascularization
	Corneal glue/tectonic keratoplasty	For perforation
	Lamellar or penetrating keratoplasty	For scar

Figure 3. Lid margin cleaning is the most important procedure. (*a*) After having applied warm compresses to the eye lids the lid margin can be cleaned either *a* with a cotton bud/swab soaked in water, with or without baby shampoo/bicarbonate, (*b*) with a flannel wrapped tightly around index finger and soaked in water, with or without baby shampoo/bicarbonate or with commercial lid wipes. (*c*, *d*) A nurse should instruct parents and children in how to safely apply drops/ointment to the eye.

Massage of the lid margin, using a finger or cotton bud, is thought to improve the outflow of meibum. This can then be followed by physical cleaning of the posterior lid margin and the base of the eye lashes with a moistened cotton bud or, in smaller children, a moistened flannel held taut over the index finger. Although advice is often provided to use water which

has been boiled, there is no evidence that the use of unsterilized tap water is harmful nor is there evidence that saline is better than water. There is limited evidence whether either home-made (e.g. diluted baby shampoo, bicarbonate of soda solution) or proprietary (e.g. hypochloric acid 0.01%) products containing mild detergents or astringents enhance the effectiveness of plain water or saline [6]. Similarly, the role of steam goggles in children is unclear. Lid hygiene, usually undertaken once to twice daily, takes several weeks to have an effect and long-term treatment is often required to prevent relapse and can be extremely difficult or impossible to perform in small children; older children should be supported to perform this themselves. It is very important for clinical staff to spend the time carefully explaining the lid hygiene technique to the child (if age appropriate) and the family, to ensure it is performed using the right method.

5.3. Antibiotics

Both topical and systemic antibiotics have been used in the treatment of BKC [32,33].

5.3.1. Topical antibiotics and antiseptics

Short-term use of topical antibiotics may be required when there is blepharitis-related acute infection of the lids, such as styes and infected meibomian cysts, but active infection is not a major component of BKC. The main rationale for using topical antibiotics (either on the lid margin after hygiene or instilled in the eye) for BKC is to reduce bacterial colonization of the lid margin. Chloramphenicol drops or ointment, erythromycin ointment, or azithromycin drops have all been used (level of evidence 4) [34]. Whilst chloramphenicol and erythromycin can be applied twice daily for prolonged periods, the optimal application schedule for topical azithromycin in BKC is unknown. Topical azithromycin has a long tissue half-life. Animal models have shown that after multiple applications of azithromycin 1.5%, tissue levels remained above the minimal inhibitory concentration for common ocular bacteria for up to a week [35]. Treatment at intervals has therefore been used in childhood BKC and adult blepharitis. Only one study on childhood BKC is available, which used a 6-month course: in the first and second month, azithromycin was administered twice daily for 3 days starting on day 1, 11, 21 (and no treatment between these cycles); in the third and fourth month, twice daily for 3 days starting on day 1 and 15; and finally in month 5 and 6, twice daily for 3 days starting on day 1 [36]. Stinging and ocular surface irritation are the most frequent adverse events [37] and can require discontinuation of the treatment [36]. In a multicenter open-label study, Haque et al. report that in adults azithromycin 1% causes a significant decrease in coagulase-negative staphylococci and corynebacterium bacterial colonization and a significant improvement in clinical signs and symptoms (level of evidence 4) [38]. In a prospective, observational, open-label clinical trial of topical azithromycin, Foulks et al. showed that in adults, the spectroscopic behavior of the meibomian gland lipids as well as clinical signs of MGD improves after therapy (level of evidence

4) [39]. A combined treatment of children with dexamethasone and azithromycin was reported to be safe [40].

Lid cleaning with chlorhexidine 0.02%, an antiseptic, may help if there is severe lid margin inflammation (level of evidence 4) [20]. Topical metronidazole (0.75% or 1%) gel can help facial skin disease [41]. It is not clear how long topical antibiotic use should continue and whether a short course is sufficient or whether longer term chronic treatment is required in both adults and children.

5.3.2. Systemic antibiotics

An effect of oral antibiotics in controlling symptoms in adults with ocular rosacea and MGD has been shown in several clinical studies (level of evidence 5) [23]. Oral antibiotics are usually used long term (at least 6–12 weeks) in low-dose (sub-antimicrobial) levels. Patients with active BKC or visually significant keratitis should be treated with long-term low-dose oral antibiotic and a course of an oral antibiotic should also be considered if there is marked blepharitis that is difficult to control with simple measures or there have been recurrent meibomian cysts. Erythromycin is the macrolide most commonly prescribed to children at doses ranging from 12.5 to 40 mg/kg body weight per day (level of evidence 4) [42]. The reported duration of systemic antibiotic treatment ranges from 1 to 23 months [18]. Clarithromycin has also been successfully used to treat BKC [23]. Newer macrolide antibiotics such as azithromycin may be as effective as erythromycin and have a longer half-life with greater tissue accumulation, allowing for less frequent administration [43]. From the age of 12 years, tetracyclines can be used. There are no published evidence-based recommendations for the dose or duration of tetracyclines in the treatment of children with MGD or BKC. Oxytetracycline can be used (500 mg t.i.d for a period of 4 months and 250 mg t.i.d. for a period of 8 weeks or longer); alternatively, many patients find it more convenient to use 100 mg doxycycline o.d. for 4 weeks followed by 50 mg o.d. for 8 weeks (can be used longer). Lower doses may be as effective. Though anti-inflammatory effects may be observed after 6 weeks of antibiotic treatment, the latency might be longer. Therefore, we recommend a minimum treatment of 12 weeks.

The mechanism of action for long-term low-dose oral macrolides and tetracyclines is unknown, but may include both an antimicrobial and an anti-inflammatory effect, inhibiting lid margin bacterial lipase activity that alters meibum composition and releases pro-inflammatory mediators from meibum [6,44].

The most common side effects of tetracyclines are diarrhea, nausea, headache, photosensitization, vaginal or oral candidiasis, and hypersensitivity [6]. Tetracyclines should not be prescribed for children less than 12 years of age due to the risk of staining of the dental enamel. Macrolides are usually well tolerated but can also cause gastrointestinal disturbances [42]. Other oral antibiotics (e.g. amoxicillin–clavulanate, cephalosporins) are sometimes used, including when there is intolerance or allergy to the more commonly used antibiotics, but the effectiveness and mechanisms of action of these have not been established [34].

5.4. Topical corticosteroids

Topical corticosteroids are the most effective initial treatment to control ocular surface inflammation for the majority of patients with BKC (level of evidence 4) [3,4,6]. A short course of intensive treatment (e.g. prednisolone 1% or dexamethasone 0.1% two hourly) may be required to control severe inflammation. Where long-term treatment (i.e. for more than 2 months) is required, it is sensible to use a product with a low risk of causing ocular hypertension and cataract, e.g. fluorometholone 0.1%, loteprednol, or rimexolone, and to rapidly taper steroids to the lowest dose compatible with symptom relief. The intraocular pressure should be monitored even with very low-dose therapy, but this can be challenging in very small children. Other possible side effects include cataract and the vulnerability to ocular surface infections, especially herpes simplex keratitis.

The risk of steroid-induced ocular hypertension following topical application of corticosteroid has been reported to be as high as 50–60% [45]. Loteprednol etabonate has been demonstrated to be safe in pediatric subjects [46] and as effective in the reduction of signs and symptoms as prednisolone acetate with less risk of increasing the intraocular pressure [2,47]. Treatment with a combination of loteprednol etabonate 0.5%/tobramycin 0.3% may be as effective as the treatment with dexamethasone 0.1%/tobramycin 0.3% (level of evidence 1b) [48], but aminoglycosides can cause toxicity following prolonged use. A sub-tenon's injection of triamcinolone acetonide has been used in noncompliant children (level of evidence 4) but this can cause problems if there is a consequent steroid-related intraocular pressure rise [49].

5.5. Calcineurin inhibitors

Topical ciclosporin or tacrolimus are alternatives to topical corticosteroid to control ocular surface inflammation and have a steroid-sparing effect. However, the use of these products for the treatment of BKC is off license. In the USA, ciclosporin A (CSA) 0.05 % (Restasis®, Allergan) and in Europe, CSA 0.1% (Ikervis®, Santen) are approved for the treatment of dry eye disease. In the United Kingdom, some specialist centers also use the veterinary CSA ointment (Optimmune 0.2%) in a special arrangement for named patients; prior to this, it was common to use local pharmacy produced 2% CSA dissolved in maize oil.

Calcineurin inhibitors are immunosuppressive agents that inhibit cell-mediated immunity and are used to treat a wide range of inflammatory and immune-mediated diseases [50]. CSA forms a complex with intracellular cyclophilin A, resulting in the inhibition of calcineurin. This prevents T cells from producing pro-inflammatory agents such as TNF-α, INF-γ, interleukin-4, and interleukin-2 which mediates activation and proliferation of T cells. CSA has a slower onset of effect than topical corticosteroid and so patients may require supplementary corticosteroid initially for severe inflammation or rapid symptom relief.

5.6. CSA

In ophthalmology, topical CSA is used for the treatment of chronic inflammatory conditions in adults (e.g. blepharitis,

MGD, rosacea keratoconjunctivitis, atopic keratoconjunctivitis, Thygeson's superficial punctate keratitis, adenoviral opacities, chronic corneal allograft reaction) [34]. CSA 0.05% has been shown to be effective in adult patients with MGD in a number of randomized, controlled trials (level of evidence 1b). CSA 0.05% has been shown to be significantly more effective than tobramycin/dexamethasone [51].

5.7. Tacrolimus

Tacrolimus (Protopic 0.03%, Astellas Pharma) is a macrolide lactone. Its potency is reported to be a factor of 10 greater than CSA [52]. Topical tacrolimus is approved for the treatment of moderate-to-severe atopic dermatitis in adults recalcitrant to glucocorticoids. Pimecrolimus (Elidel® 1%, MEDA PHARMA) is approved for the treatment of mild-to-moderate atopic dermatitis in children aged 2 years and above. It acts more selectively than tacrolimus and has lower skin penetration. In a retrospective case series of adult patients with atopic blepharoconjunctivitis looking at application of therapy to the lid skin, tacrolimus was more effective and better tolerated than pimecrolimus without any induced ocular hypertension, cataract formation, lid skin atrophy, or malignant transformation (n = 338, mean follow-up 5.7 years) [53]. Tacrolimus ointment (0.03%) instilled in the eye has been reported to be effective for the treatment of atopic blepharoconjunctivitis (n = 20, mean age 10.8 years); however, the pathophysiology of this differs from nonatopic BKC [48]. Reported adverse events of treatment with topical calcineurin antagonists are rare. Lid maceration was reported in one patient treated with topical CSA 2% [49,54]. Tacrolimus as well as pimecrolimus are known to cause transient local burning and can possibly induce herpetic keratitis [52].

The use of systemic immunosuppression at doses for suppression of allograft rejection is associated with a risk of lymphoma, skin tumors, and granulomatous lymphadenitis [55]. However, the risk of topical application is debated [56]. In 2005, the Pediatric Advisory Committee of the US FDA warned about treatment with topical calcineurin inhibitors, considering the lack of long-term safety data and the potential risk of malignancies. There are two studies in adults, published in 2015. A systematic literature search and a separate meta-analysis on case control and cohort studies reported that topical treatment with calcineurin inhibitors of atopic dermatitis was unlikely to be a significant risk factor for lymphoma [51]. In contrast, a longitudinal post-marketing study identified 5 out of 7457 children treated with pimecrolimus due to atopic dermatitis who developed a malignancy such as leukemia (2), osteosarcoma (1), and lymphoma (2); local skin malignancies were not detected. The authors considered the treatment unlikely to be associated with an increased risk of malignancy [57]. Conjunctival squamous cell carcinomas were reported after systemic treatment with CSA which has created concerns that its topical application might have a similar effect on the ocular surface. In a retrospective interventional case series, 76 eyes treated with CSA 1% or 2% for a mean period of 2.2 years did not show any microscopic or cytological signs of malignant transformation after a mean follow-up of 5.9 years [58]. CSA was undetectable in peripheral blood after topical

treatment with concentrations of 0.05% or 0.1% for 12 months [59]. Similarly, the treatment of 156 children with vernal keratokonjunctivitis with concentrations of 1% and 2%, respectively, was reported to safe (mean duration of treatment 3.8 ± 1.09 years) [54,60]. Considering these results and their potential steroid-sparing effect, calcineurin inhibitors seem to be safe and effective in the treatment of BKC but there is still some concern about the lack of extensive randomized clinical trials or very long-term effects after use in children with BKC.

5.8. Systemic immunosuppression

Systemic immunosuppression for BKC should be considered if there is inexorable corneal vascularization with opacification, or corneal melt with threatened or actual perforation [18], and also to control inflammation and reduce the risk following keratoplasty or other significant ocular surface surgery. Options include prednisolone, azathioprine, mycophenolate mofetil, or CSA (level of evidence 4) [20]. Pediatricians should be involved and patients may need to be screened for tuberculosis (Quantiferon) and immunity to herpes zoster.

5.9. Ancillary treatment: artificial tears and dietary modification

Dry eye with punctate corneal epithelial erosions occurs secondary to lid and conjunctival inflammation. Topical lubricants may support the integrity of the tear film, keep tear osmolarity close to physiological levels, and dilute inflammatory agents. They may be a helpful ancillary treatment option for symptom control (level of evidence 5 in adults), particularly in older children; care must be taken not to overburden the family with numerous eye drops [4]. Preservative-free preparations may be less liable to cause secondary symptoms of ocular surface toxicity if frequent application is required [61].

The use of oral omega-3 (e.g. flaxseed oil, fish oil) has been recommended as an ancillary treatment for the control of ocular surface disease [21]. Experiments in a murine dry eye disease model suggest that polyunsaturated fatty acids of omega-3 and omega-6 might act as naturally occurring anti-inflammatory agents and reduce inflammatory cytokine expression [62]. In clinical trials in adults with MGD, the oral intake of omega-3 was shown to suppress the systemic production of pro-inflammatory cytokines and eicosanoids (TNF-α, IL-1b, thromboxane B2, prostaglandin E2) [63]. They may also affect the polar lipid profiles of meibomian gland secretions [64]. However, it is unclear whether these observations relate to the disease mechanisms of BKC and whether any benefit might be expected to accrue in BKC from diet supplementation.

There are few reports on their use in BKC (level of evidence 4) [21]. In moderate and severe BKC, the anti-inflammatory effect of omega-3 supplements alone may not be sufficient to control inflammation [65] but patients often report improvement and some ability to reduce other treatment modalities. To date, there are no data comparing the efficacy and safety of oral omega-3 supplements with other anti-inflammatory drugs such as steroids or calcineurin antagonists. The potential side effects of the long-term use of flaxseed oil in children are unknown and, although a maximum treatment of 6 months has been suggested, there is no evidence to support this [20,66–68].

6. Severe complications of BKC

Secondary microbial keratitis is rare and should be treated with intensive broad-spectrum topical antibiotics. An axial corneal opacity or irregular astigmatism may cause amblyopia in younger children. Glasses and, if necessary, occlusion for amblyopia should be prescribed and visual correction may be improved in older children with a rigid contact lens. Lamellar or penetrating keratoplasty may be required for severe corneal scarring that is significantly reducing the vision but is much higher risk in both children and in those with active ocular surface inflammation. Attempts can be made to reduce corneal neovascularization using fine needle diathermy or subconjunctival anti-vascular endothelial growth factor agents [69]. Corneal perforation (Figure 4) should be managed in the short term with bandage contact lenses if minor and potentially self-healing, or cyanoacrylate glue but tectonic keratoplasty may be required (level of evidence 4) [18].

7. Conclusion

BKC is an important cause of ocular morbidity in childhood. It is under-recognized and there is often a substantial delay in diagnosis and the initiation of treatment. There is no current evidence-based consensus on the management of BKC. Interventions target the specific manifestations affecting lids, conjunctiva, and cornea. Drug treatment options include topical steroids and immunosuppressants and topical and systemic antibiotics to control inflammation. Lid hygiene, dietary modification, and tear supplements have an uncertain role but are low risk. MGD, bacterial colonization of the meibomian glands, hyperosmolarity of the tear film, and upregulation of inflammatory cytokines may be involved in the development of BKC. Further research is required to determine the pathogenesis, and thus guide the management, of BKC and potentially help define pathways of therapy for different subgroups of disease.
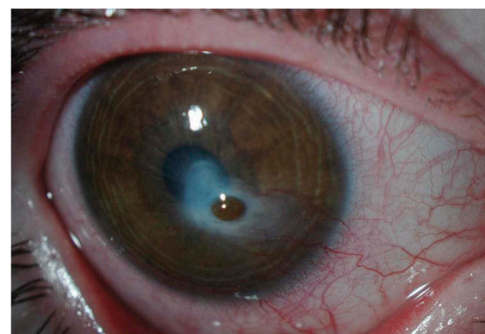

Figure 4. Corneal perforation with protruding iris in a child with acute keratitis. A similar but less severe defect was located in the same position of the left eye (not in picture).

8. Expert commentary

BKC is a common eye disorder in children, although the prevalence is unknown. There is little high-quality evidence to support the superiority of any specific therapy for BKC and this is particularly so for pediatric BKC. Treatment and theories of pathogenesis are based on the assumption that the mechanisms of BKC and rosacea keratitis are the same which may or may not be justified. The diagnostic criteria are poorly defined and the importance of clinical subgroups is unknown. There are no generally accepted grading scales, hampering the quantitative assessment of different treatments in clinical trials. Accordingly, treatment guidelines are based on limited evidence.

We tailor treatment to address the specific lid, conjunctival and corneal signs, and the severity of inflammation (Table 1). It is important to modify the approach to disease from that in adults to ensure compliance and to retain engagement of the patient and their family.

The treatment of acute stages of disease activity with steroids is unspecific and exposes the patient at risk of various detrimental ocular side effects. CSA is not licensed for this indication but is effective in clinical practice, although there are some potential concerns on very long-term use and the possibility of later local malignancy. Randomized clinical trials are needed to evaluate the role of the different steroid-sparing immunomodulators. Also, the role and effects of osmoprotectants and essential fatty acids need further investigation, since they might serve as valuable additive treatment options with minimal risk for adverse effects.

9. Five-year view

We believe that within the next 5 years, the goals should be

- to agree a classification of the clinical signs of BKC according to severity of disease,
- to use this classification to develop and evaluate treatment pathways, and
- to develop a framework for randomized clinical trials of key treatments to guide therapy.

Key issues

- In developed countries BKC is probably second only to allergic eye disease as a reason for referral to external eye disease services. However, the prevalence is unknown.
- The mean of age of onset is between 4 to 5 years. Girls, South Asian and Middle-Eastern children are affected more frequently. There is characteristically a significant delay between the onset of symptoms and diagnosis.
- In a minority of patients there can be sight threatening complications such as corneal thinning, stromal scarring and perforation; this is more likely and more serious in childhood than in adults with blepharitis. In younger patients corneal opacity can result in visual deprivation amblyopia.

- A grading of the relative severity of clinical signs such as diffuse conjunctival inflammation, phlyctenules, corneal inflammation, scarring and vascularization has not been agreed. Such a grading would help develop treatment pathways and support robust clinical trials.
- Hypotheses for the pathogenesis of BKC and pathways for treatment are largely based on research on blepharitis and experience treating adult rosacea and rosacea keratoconjunctivitis. The assumption that there is a shared pathogenesis between these conditions may not be valid.
- Treatment with topical corticosteroids and antibiotics is effective in most cases. Monitoring for unwanted side effects of treatment is essential and can be more challenging in children. Treatment may be required for several months.
- Topical and systemic antibiotics may be used singly or in combination. Chloramphenicol, erythromycin and azithromycin are suitable for topical application. Macrolides and tetracyclines are used for systemic treatment. Tetracyclines should only be used in children after the age of 12 years. Erythromycin is a good alternative for younger children. Recent reports suggest that azithromycin may be more effective.
- Randomized clinical trials are needed to evaluate the relative benefit of calcineurin inhibitors compared to topical corticosteroid. Essential fatty acids might serve as valuable anti-inflammatory treatment options.

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