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Review article

Pediatric blepharokeratoconjunctivitis: A challenging ocular surface disease

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ABSTRACT

Pediatric blepharokeratoconjunctivitis (PBKC) is a chronic and recurrent ocular surface inflammatory disorder affecting children in early life. It is frequently under- or late- diagnosed, representing a potential cause of severe visual morbidity worldwide. An expert panel consensus recently agreed on its definition and proposed diagnostic criteria for suspected and definitive PBKC to reduce confusion and avoid varied terminology previously used in the literature, improving early and precise diagnosis. Previous evidence has pointed to the role of the adaptive immune system in recognizing and handling antigenic eyelid bacterial products, particularly from the cell wall, and the direct toxic and inflammatory effects of their cytolytic exotoxins on the ocular surface. PBKC is a frequent referral in pediatric and cornea clinics characterized by a history of recurrent chalazia, blepharitis, meibomian gland dysfunction, conjunctival hyperemia, phlyctenules formation, and corneal infiltrates with vascularization and scarring. The latter is a major cause of significant visual loss and amblyopia. Current treatment strategies aim to control inflammation on the ocular surface, halt disease progression, and avoid corneal involvement. Further research on pathogenic mechanisms will shed light on novel potential therapeutic strategies. Awareness of PBKC should enhance early diagnosis, prompt adequate treatment, and improve outcomes. We compile current evidence on epidemiology, pathophysiology, clinical spectrum of disease, diagnostic criteria, and management strategies for PBKC.

1. Introduction

The recently agreed definition of pediatric blepharokeratoconjunctivitis (PBKC) by the PBKC Study Group defines this entity as follows: "Pediatric Blepharokeratoconjunctivis is an underdiagnosed, sight-threatening, chronic, and recurrent inflammatory ocular surface disease affecting children and adolescents. Its clinical spectrum includes chronic blepharitis, meibomitis, conjunctivitis, and corneal involvement ranging from superficial punctate keratitis (SPK) to corneal infiltrates with vascularization and scarring."[126] PBKC is a more frequent condition than thought, accounting for 15–25 % of pediatric corneal referrals.[71] It is a multifactorial disease with a natural course that might end up in irreversible corneal damage in up to 81 % of the affected eyes,[115] resulting in leukoma formation, irregular astigmatism, higher-order aberrations, stromal degradation, and corneal perforation, eventually leading to permanent vision loss or amblyopia in youngsters.[65,87,120,155,198]

Due to nonspecific symptoms and signs shared with many other ocular surface inflammatory conditions and poorly understood etiology and pathogenic mechanisms, PBKC has been referred to by many different terms in the literature. Among the most common names used to refer to PBKC are Staphylococcal blepharokeratoconjunctivitis, blepharokeratoconjunctivitis in childhood, childhood or pediatric ocular rosacea, Staphylococcal blepharoconjunctivitis, and meibomitis-related

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keratoconjunctivitis (MRKC).[126,185] A systematic review by Suzuki and coworkers concluded that pediatric ocular rosacea, phlyctenular keratoconjunctivitis (PKC), MRKC, and PBKC belong to a similar clinical disease category, favoring an inclusive broad clinical spectrum encompassing these pathologies.[185] Recently, a Delphi consensus unified and clarified its nomenclature and definition and gave definitive and suspect diagnostic criteria to avoid terminology confusion and reduce the under- and misdiagnosis of the disease.[126] We provide an up-to-date overview of PBKC epidemiological features, the current evidence on its pathogenic mechanisms, the spectrum of clinical manifestations, risk factors for severe corneal involvement, diagnostic methodologies, treatment alternatives, complications, and the visual outcomes reported in the literature.

2. History and background

The earliest description of blepharitis occurred in 1894 when Lydston described a "microbic or chemical irritation induced by the extrusion of the decomposed secretion from the meibomian glands."[112] More than a decade later, Elschnig[52] described the symptoms of meibomian glands (MG) hypersecretion and the relief after emptying the glands with astringents. In 1921, Gifford isolated *S. aureus* and *B. xerosis* from MG secretions and proposed the first classification for meibomian gland disease.[64] Among the initial PKC reports, Casparis described the disease in the American Journal of Diseases in Children, remarking that a tuberculin hypersensitivity reaction produced phlyctenules.[21] In 1942, Scobee recognized the frequent isolation of staphylococci from MG cultures in conjunctivitis patients and normal controls, suggesting a role in the pathogenesis of chronic blepharitis.[166] He recommended a therapy of lid massage in combination with adrenalin and antiseptic eyedrops to improve the condition.[166] In 1946, Thygeson classified the disease into different types according to its etiology.[193] Thirty years later (1977), Smolin and Okumoto made a complete clinical and pathogenic compendium of knowledge of staphylococcal blepharitis.[171] In 1982, McCulley and coworkers proposed a modern categorization that led to further insight into chronic blepharitis.[116] In the 1990s, significant efforts by Ficker's group in London led to an improved understanding of Staphylococci's pathogenic mechanisms.[55,56,167] A decade later, the group led by Suzuki and Kinoshita in Kyoto identified the association between *Cutibacterium acnes* [*C. acnes*], (previously known as *Propionibacterium acnes* [*P. acnes*]), meibomitis, and corneal infiltration, originating the term MRKC.[180,182,183,185] On the clinical side, PBKC has seen an ever-growing interest reflected in the increased number of reports (*see* Table 1) since Viswalingam and coworkers presented their findings on the epidemiology, clinical features, and morbidity of the disease in the 1997 Annual ARVO Meeting.[199]

3. Epidemiologic features and visual impact

PBKC is more common than reported. Among pediatric eye clinics, it has been estimated to account for 12–15 % of patient referrals.[33,34,67,71] Most cohort studies, however, are from tertiary eye care centers and do not reflect the true prevalence of the disease. Although cohorts including Hispanic,[155] Indian,[67] Asian,[191] Middle Eastern,[198] and Caucasian patients[41,69] report the prevalence and severity among those ethnicities, no studies address ethnic prevalence differences. Regarding gender distribution, several studies report a female predominance (up to 87 %),[65,71,182,185,191,198] while others found no difference between males and females.[51,62,65,87] The mean age of onset ranges from 1 to 14 years,[198] but the diagnosis is usually established between 3 and 9 years, depending on the series.[87,155] Risk factors and associated conditions include poor hygiene, seborrheic dermatitis, history of atopy, infestation with

Table 1
Representative literature reports on pediatric blepharokeratoconjunctivitis.

Author	*Country*	*No. of patients*	*Gender ratio (F: M)*	*Mean follow-up (months)*	*Mean age at diagnosis (years)*	*Recurrent chalazia (%)*	*Corneal involvement* (%)*	*Mean BCVA at the end of follow-up (Log MAR)*	*Amblyopia (%)*
Gupta et al. [27]	India	615	1:1.6	NA	6.7	18.2 %	5 %	NA	NA
Moon et al.[35]	Korea	137	1.9:1	20.4 ± 28.8	9.5 ± 3.6	38 %	77.4 %	0.2 ± 0.3	8.8 %
Gonzalez-Godinez [5]	Mexico	114	1:1	26.4 ± 25.2	9.3 ± 4.2	30.7 %	39.5 %	0.16 ± 0.18	6.14 %
Kaufman et al. [36] * *	United States	70	1:1.69	38.3 ± 45.4	6.9 ± 4.1	47.1 %	67.4 %	NA	16.8 %
Teo et al. [28]	Singapore	51	4.1:1	58.9	10.2	45.1 %	100 %	0.2	NA
Gautam et al. [33]* *	Nepal	50	1:1.1	NA	8.0 ± 6.2	NA	0 %	NA	NA
Viswalingam et al.[4]	United Kingdom	44	1.2:1	84	5.4	15.9 %	63.6 %	NA	NA
Audelan et al. [37]	France	42	NA	NA	10.17 ± 3.28	79.7 %	57 %	NA	NA
Hammersmith et al.[38]	United States	29	1.2:1	5.4	6.5	73 %	52 %	NA	7 %
Jones et al.[7]	United Kingdom	27	1:1	27.6	6.9	67 %	81 %	0.02 (median)	30 %
Jo et al. [39]* *	Korea	26	2.25:1	NA	18.4 ± 10.5	NA	80 %	0.29 ± 0.30	NA
Suzuki et al. [22]* *	Japan	23	6.6:1	NA	17.91 ± 7.84	56.5 %	100 %	NA	NA
Doan et al. [30]	France	23	4.7:1	228 ± 48	7 ± 3	NA	65 %	0.09	30 %
Donaldson et al. [40]	United States	20	2.3:1	19.6	9.2	NA	80 %	NA	NA
Wu et al. [41]	China	18	3.5:1	NA	10.2 ± 3.8	67 %	61 %	NA	NA
Donmez et al. [42]	Turkey	16	3:1	52.8 ± 52	7.7 ± 5	75 %	37.5 %	NA	NA
Elbaz et al. [43]	Canada	11	1:1.2	NA	12.4 ± 3.7	NA	36.6 %	NA	NA
Hamada et al. [29]	United Kingdom	10	1:1	52.8	9.4	5 %	70 %	0.14	NA
Farpour et al. [44]	Australia	8	1.6:1	8.3	3.2	NA	50 %	NA	NA

BCVA: Best-corrected visual acuity, PBKC: Pediatric blepharokeratoconjunctivitis, NA: Not available.
*Defined as pannus formation, phlyctenules, corneal neovascularization, corneal perforation, and/or scarring.
* * These case series described patients with phlyctenular keratitis only.

Demodex mites,[4] and high *C. acnes* detection rates in meibum culture.[180] Table 1 summarizes the most relevant worldwide PBKC case series reported in the literature.

4. Pathophysiology evidence

The pathophysiology of PBKC is complex, involving interaction between innate immune mechanisms, adaptive immunity, and vascular biology; thus, vascular dysregulation and altered immune response to putative antigens, including those from eyelid margin bacteria (i.e., *Staphylococci, Cutibacterium, Mycobacteria*) with their consequent inflammatory changes play a significant role in the eyelids and the ocular surface inflammatory changes observed during the clinical course of PBKC.[34]

PBKC begins as an eyelid margin disease with anterior blepharitis, posterior blepharitis (meibomitis), and recurrent chalazia. These alterations lead to a recurrent inflammatory reaction through several hypothesized mechanisms, with ensuing blepharoconjunctivitis and corneal damage.[19]

The precise underlying mechanisms of PBKC disease are not fully understood. Early polymicrobial colonization in humans is primarily caused by *Staphylococcus aureus* and other *Staphylococcus spp.*, Corynebacteria, and Propionibacteria (*C. acnes*).[30] In particular, *S. aureus* is one of the foremost opportunistic bacterial pathogens in humans, causing significant morbidity after persistent colonization of the nose mucosa, eyelids, and skin, among other tissues.[96]

Previous studies hypothesized that immunogenetic susceptibility, together with an early anomalous bacterial presentation to an immature immune system in the eyelids early in life, facilitates an imbalance in the bacterial flora of the eyelids.[43,44,54]

Furthermore, there are recently described *S. aureus* immune evasion molecules, specifically phenol-soluble modulins (PSMs) that induce neutrophil lysis and extracellular adherence proteins (EapH1 and EapH2), which inhibit the secretion of neutrophil serine proteases (NSPs).[95,173,175] *S. aureus* also secretes a range of superantigens, including staphylococcal superantigen (SElW) and the bifunctional staphylococcal enterotoxin-like toxin X (SElX) that binds to neutrophil surface receptors inhibiting phagocytosis and leading to lymphocyte-T proliferation and immune dysregulation.[95,173,175,176] Additionally, *S. aureus* secretes staphylococcal peroxidase inhibitor (SPIN), which inhibits myeloperoxidase (MPO) phagosomal killing activity through the generation of reactive oxygen species (ROS).[36,149] The immune alterations described above, in combination with *S. aureus* immune evasive properties could be responsible for allowing an increased proliferation of bacterial colonies at the external eyelid margin, perpetuating the potential generation of hypersensitivity reactions against essential products of the bacterial cell wall, mainly Staphylococcal protein-A and the teichoic acids (i.e., ribitol and glycerol), along with the direct inflammatory effect of their exotoxins (α−, β−, and γ-lysins) on the ocular surface. These antigenic molecules may manifest as a cell-mediated immune response (CMI) and an "enhanced" delayed-type hypersensitivity (DTH) reaction.[17,24,34,56,80,160,198]

Additionally, little is known about microbiome changes in the eyelid margin and the tear film biomarkers (i.e., cytokines, chemokines, proteases) profile expressed during the active stage of PBKC. Such information would be valuable in better understanding its pathogenesis. The same is true for the innate and adaptive humoral and cellular immune reactions occurring during acute conjunctivitis and keratitis related to the disease.

4.1. Vascular changes and eyelid margin alterations

PBKC leads to chronic eyelid inflammation and potential telangiectasia formation. Also, some patients with PBKC may develop rosacea-like skin manifestations such as facial erythema, telangiectasia, flushing, papulopustular rash, and phymatous changes.[17,24,31,80,126] Such vascular changes increase the facial skin temperature, especially during flushing,[170,203] and may alter coagulase-negative Staphylococcis behavior, intensifying their virulence and increasing inflammation.[170] In PBKC, meibomitis leads to altered meibum secretion, recurrent chalazia, glandular atrophy, and thickened eyelid margins.[129] It is still unclear if inflammation is a cause or a consequence of MGD and whether the biochemical changes observed in meibum composition are primary or secondary to microbial interactions, including lipase activity.[33,57] As described in the adult population, the alteration of meibum composition in chronic blepharitis is characterized by an increase of monounsaturated fatty acids from wax/sterol esters compared to healthy subjects.[47] Also, keratinization of epithelial cells obstructs the gland's opening and causes intraglandular cystic dilation, gland atrophy, meibocyte loss, and altered meibum.[13,68,82,131] Interestingly, the histopathological analysis of obstructed MGs shows a marked absence of intraglandular inflammatory cells, supporting the notion that keratinization is one of the primary components of obstructive MGD.[94,136] Such composition changes also alter the melting point of meibum, leading to a high-viscosity oil mixed with desquamated epithelial cells.[94] Typically, chronic eyelid alterations precede conjunctival and corneal damage.

4.2. Microbial interactions on the eyelid margin

Abnormal colonization of *Staphylococcus spp., C. acnes,* and *Demodex folliculorum,* among other bacteria, may be implicated in PBKC.[27,34,105] *Staphylococcus spp.* is involved in direct ocular surface inflammation through the biochemical decomposition of meibum by lipase activity and its exotoxins, including α-, β-, and γ-lysin.[109,167] These lytic and cytotoxic exotoxins may induce corneal epithelium damage in the form of SPK (see *Section 5 . Clinical manifestations*) accompanied by an unstable tear film. Exfoliative toxins produced by these bacteria can damage the epidermis and exacerbate the inflammation associated with chronic blepharitis.[58,167] Also, superantigens produced by staphylococcal bacteria can activate T-lymphocytes, leading to a systemic inflammatory response.[45]

S. epidermidis, *S. aureus*, and *C. acnes* have been consistently isolated from lid swab cultures in patients with PBKC.[45,54,67] This altered microbial microenvironment leads to increased bacterial lipase activity, changing the quality of the meibum, increasing free fatty acids,[112] and favoring the continual growth of bacteria on the eyelid.[118] The role of lipase activity was also demonstrated by Dougherty and coworkers, who reported inhibition of lipase production after administration of tetracycline in tetracycline-resistant strains of *S. epidermidis*.[46] This inhibitory effect partially explains the clinical improvement observed in patients with chronic blepharitis, even with antimicrobial doses under minimum inhibitory concentration.[46]

C. acnes is an anaerobic gram-positive bacillus frequently isolated from normal skin and follicles.[183] Suzuki and coworkers have hypothesized the potential pathogenic role of *C. acnes* in PBKC, specifically meibomitis-related keratoconjunctivitis (MRKC), demonstrating their inflammatory capacity via DTH reactions in the form of phlyctenule formation on the cornea.[180,182–185] Compared to healthy controls, *C. acnes* is also predominant in meibum cultures in patients with phlyctenular keratitis associated with meibomitis.[182]

Demodex folliculorum and *brevis* are probably also implicated in the pathogenesis of PBKC. Since *Demodex* is highly prevalent among the population, studies suggest that the mean density of mites, rather than colonization itself, is correlated with the pathogenic factor.[105] A density of 5 mites per follicle or cm^2 is considered pathogenic.[78] Additionally, *Demodex* mites may not always generate cylindrical dandruff (sleeves) in children; thus, diagnosis becomes complex without lash epilation and direct microscopic detection.[109] Wu and coworkers report that *Demodex* is more frequent in patients with PBKC and is associated with worse lid margin inflammation and MGD.[207] *Demodex* inhibits the innate immune system response, producing proinflammatory cytokines such as IL-8 and TNF-α and upregulation of Toll-like receptor 2 (TLR-2).[80] Furthermore,

Demodex bacterial endosymbionts, such as *Bacillus olenorium,* have been linked to initiating inflammatory reactions on the eyelid margin.[100] Nonetheless, the role of microorganisms in the definite pathogenesis of PBKC still needs to be elucidated. Most likely, microorganisms are synergistic in generating and perpetuating infection-inflammation processes in susceptible hosts.

4.3. Immune dysregulation

There is limited evidence of the potential implication of innate and adaptive immune systems in the pathogenesis of PBKC.

4.3.1. Bacterial lipopolysaccharides

Bacterial lipopolysaccharides stimulate the release of proinflammatory factors, such as TNF-α, interleukins, proteases, and lipases, through their interaction with the innate immune system.[80] These molecules may act as antigens and are believed to initiate type-IV hypersensitivity reactions.[55,180]

4.3.2. Upregulation of the TLR-2 pathway

TLR-2 is a pattern recognition receptor of the innate immune system that detects early pathogen epitopes. Several TLRs participate in the upregulation of antimicrobial peptides on the ocular surface.[123] The upregulation of TLR-2 occurs in response to bacterial peptides and lipopolysaccharides, matrix metalloproteinases (MMPs) expression, and cathelicidins.[37,80] TLR-2 also mediates the release of TNF-α and IL-1β, two potent proinflammatory cytokines.[168] Also, increased expression of MMPs leads to increased kallikrein 5 (KLK5), which, in turn, modulates LL-37 expression, a neutrophil granule- and epithelial cell-derived cathelicidin.[80] Furthermore, the TLR-2 pathway is known to upregulate the NF-κB complex, which could play a key role in the pathogenesis of ocular surface disorders like PBKC and rosacea.[205]

4.3.3. Overexpression of the cathelicidin LL-37

iOverexpression of the canthelcidin LL-37 nduces proinflammatory cytokines, chemotaxis, and angiogenesis.[164] LL-37 is a cathelicidin-derived antimicrobial peptide that is thought to play a crucial role in the pathogenesis of rosacea, a similar ocular surface disease to PBKC.[49,177] Although no specific treatments exist for LL-37 or cathelicidin inhibition, the vitamin D3 pathway might be a future therapeutic target that could be tried for treating PBKC;[44] however, further research is needed to elucidate the role of cathelicidins in the pathogenesis of PBKC and the potential role of vitamin D3.

4.3.4. Bacterial phospholipase-A2

Bacterial phosphlipase-A2 catalyzes the release of arachidonic acid from meibum secretions, leading to an inflammatory reaction and neutrophil chemotaxis that destabilizes the tear film, inducing hyperosmolarity, SPK and the perpetuation of dry eye and ocular surface inflammation.[34,86] Interestingly, *C. acnes* might evade the neutrophil and monocyte infiltration of the cornea, thus prolonging the DTH response.[180] *S. aureus* cell wall's protein A can induce an enhanced CMI reaction expressed as DTH with previous and repeated exposure to its antigens.[55] This "enhanced" CMI reaction generates a marked inflammatory response to a small number of staphylococcal antigens that would otherwise cause no effect.[55]

Regarding the adaptive immune response, activation, and dysregulation have also been implicated as pathogenic features of ocular rosacea.[80]

4.3.5. CD4 + :CD8 + T-lymphocyte cell ratio

Increased CD4=:CD8+ T-lymphocyte cell ratio and upregulation of Th1, Th17, IFN-γ, IL-17A, and IL-18 have been detected in rosacea patients, a disease sharing ocular surface inflammatory features with PBKC.[18,80] On the other hand. *C. acnes* has been implicated in a strong CD4 + DTH reaction in rat corneal models, suggesting a potential role in the perpetuation of corneal inflammation and a key role in phlyctenule formation.[180,182,183,185]

4.3.6. CD31 + /PECAM-1

Signaling through CD31+/PECAM-1 leads to upregulation of vascular endothelial growth factor (VEGF) and angiogenesis in the form of telangiectasia and a "highway" for an influx of proinflammatory cytokines and immune cells.[92,107] VEGF inhibitors might also be a promising therapeutic strategy in cases of corneal vascularization related to PBKC.[131]

4.3.7. B-cell (CD20 +) mediated response

A B-cell (CD20+) mediated response leads to fibrotic and phymatous changes. This response accounts for 10–20 % of the inflammatory corneal infiltrates. It leads to the production of IL-6 and TGF-β, implicating their role in the fibrotic changes seen in the eyelid margin and the rhinophyma in patients with rosacea.[80,145]

In summary, microbial interactions on the eyelid margins are hypothesized to compromise the innate and adaptive immune response in PBKC eyes, causing a cascade of inflammatory markers that lead to increased protease and lipase activity, vascular dysregulation, effector cells chemotaxis, VEGF upregulation, perpetuating the ocular surface inflammatory process in susceptible hosts. Additional research on signaling pathways of the NF-κB complex and cathelicidins, the role of other proinflammatory molecules, host susceptibility factors, antigen immune tolerance, and the waning nature of inflammation seen in puberty may shed light on the pathogenesis of PBKC (Figure 1).

5. Clinical manifestations

PBKC is characterized by a broad spectrum of clinical signs and symptoms ranging from mild palpebral manifestations to severe corneal involvement. The sudden onset of red eye, tearing, photophobia, and ocular discomfort characterizes active disease. On the other hand, chronic sequelae often lead to severe corneal scarring, irregular astigmatism, and potentially amblyopia.

5.1. Symptoms

Patients with PBKC may present with red eyes, tearing, photophobia, chronic discomfort, ocular irritation, blinking, and foreign body sensation.[44,65,66,72,155,182,191,198] They often refer to a history of early onset of recurrent chalazia, highly suggestive of PBKC. Thus, this frequently overlooked clinical manifestation should alert pediatricians and ophthalmologists to possible PBKC diagnosis.[71] PBKC can lead to severe corneal complications (see Section 5.2.4), leading to rapidly progressive vision loss.[40,67,87]

5.2. Clinical signs

5.2.1. Laterality

PBKC is considered a bilateral disease; however, a subgroup of patients may present marked asymmetry, with one eye showing significant ocular surface inflammation involving the cornea and the other showing only subtle signs of the disease on the eyelid margin. While some studies report unilateral disease (range: 3–52 %), others report equal distribution between unilateral and bilateral PBKC cases (range: 47.5–100 %).[44,65,66,72,155,182,191,198] Few reports mention the percentage of patients with bilateral involvement and asymmetric disease. Rodriguez-Garcia and coworkers observed a high percentage of asymmetrical disease (41.2 %).[155] Interestingly, patients with asymmetrical disease also had a 2-fold higher risk of developing corneal inflammation.[155]

5.2.2. Eyelids and lashes

As mentioned, a history of recurrent chalazia is a major feature of

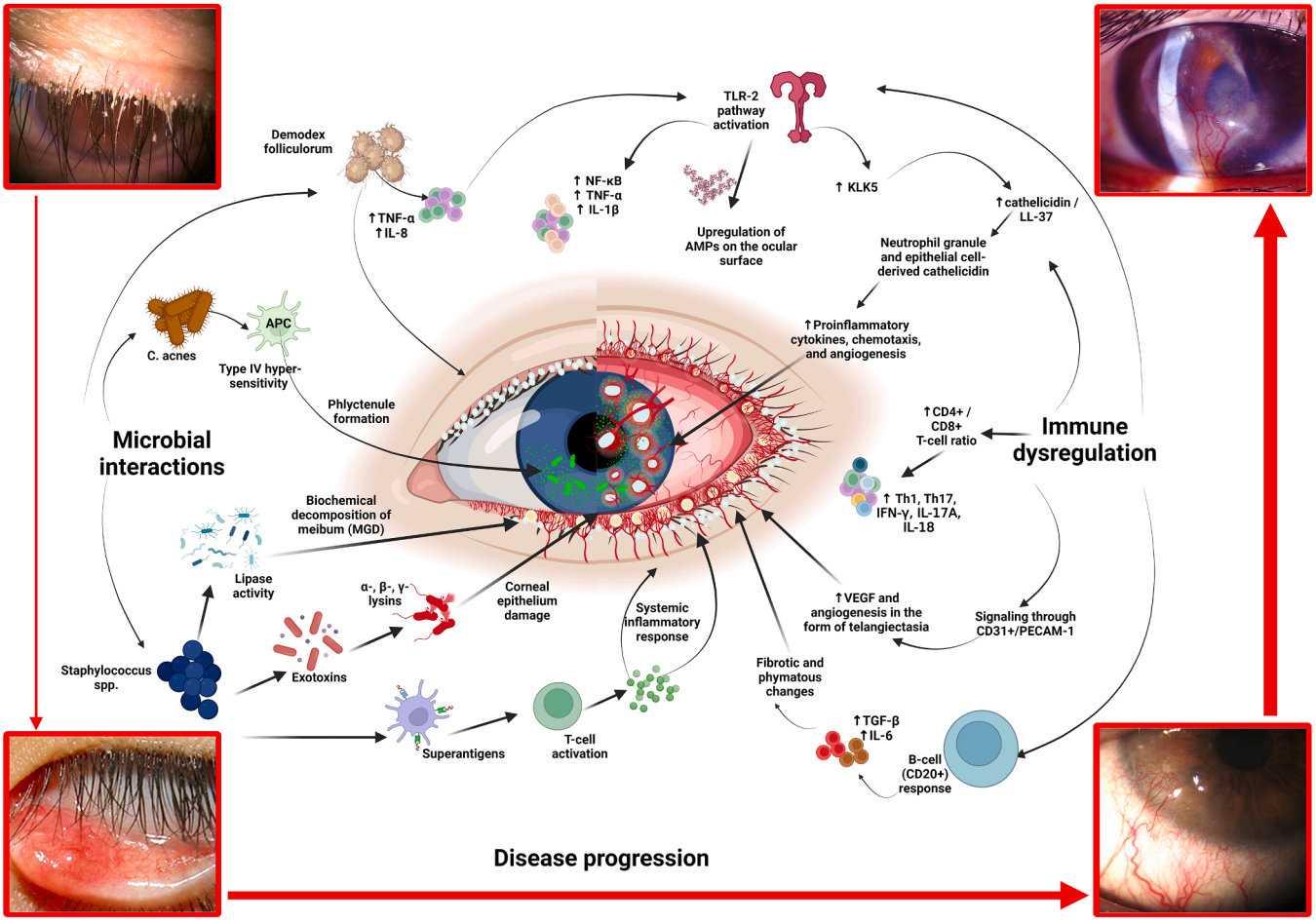


Fig. 1. Proposed pediatric blepharokeratoconjunctivitis pathogenic mechanisms based on previous research evidence.

PBKC, present in 5–75 % of patients. Hence, a history of recurrent chalazia in children should lead to a suspicion of PBKC. The pathogenesis of chalazion involves the obstruction of the meibomian glands, leading to chronic granulomatous inflammation. [155] *C. acnes* may contribute to this process by promoting a chronic inflammatory response that leads to granuloma formation.[9,181] Chronic or recurrent blepharitis is the most common palpebral manifestation.[23,44,67,72,155] Inflammation of the palpebral skin, ciliary follicles, and the base of the eyelashes is referred to as anterior blepharitis. It is frequently associated with *Staphylococcus spp*. infection. The inflammation of the posterior lid margin is known as posterior blepharitis, which affects the meibomian glands, with MGD being a potential cause.[131] Clinical findings include scurf, crusts, collarettes, meibomitis, MGD, and internal or external chalazion. Focal or diffuse meibomitis is a common feature of PBKC.[44, 180,191] Other characteristics that may be present are telangiectasia of the lid margins, lid thickening or erythema, and hordeolum (Figure 2). Chronic changes comprise lid margin keratinization and scarring or notching, telangiectasia, madarosis, and distortion or abnormal alignment of Meibomian glands.[34]

5.2.3. *Conjunctiva*

The most common conjunctival PBKC sign is hyperemia, which may have a sudden onset in cases of active disease.[43,44,54,67,155] Conjunctival papillae and follicular reactions are also part of the broad spectrum of PBKC, with papillary reactions being more frequent (Figure 3).[65] This papillary reaction affects the tarsal conjunctiva, and, similar to papillae in allergic disease, it often decreases in size with treatment but does not disappear completely. Phlyctenules in PBKC are conjunctival nodular

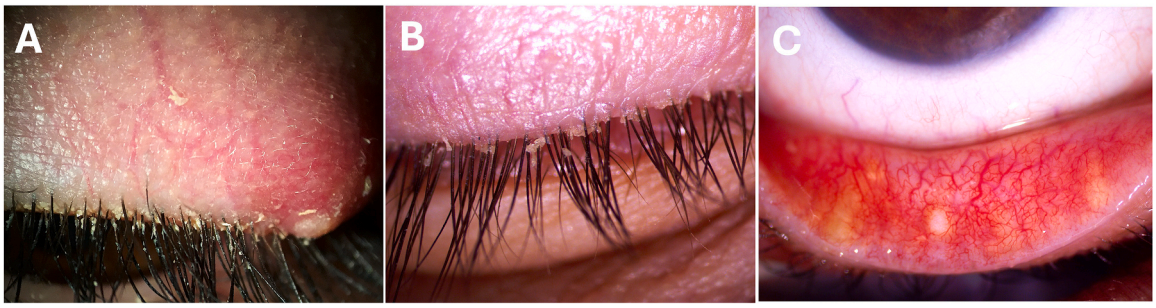


Fig. 2. Pediatric blepharokeratoconjunctivitis eyelid manifestations. **A.** Large acute external chalazion of the upper lid; **B.** Abundant collarette secretions on the anterior eyelid margin; **C.** Inferior eyelid margin and palpebral conjunctiva hyperemia and significant obstructive meibomian gland dysfunction.

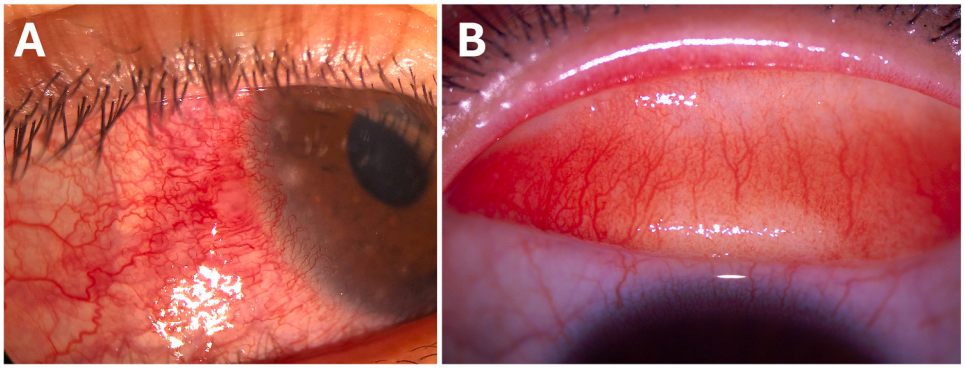


Fig. 3. Pediatric blepharokeratoconjunctivitis conjunctival manifestations. **A.** Marked bulbar conjunctival hyperemia with multiple peripheral corneal phlyctenules; **B.** Upper tarsal conjunctival papillary reaction in acute PBKC.

limbal formations invading the peripheral cornea, mainly situated in the interpalpebral fissure with or without epithelial defects that may persist, inducing superficial vascularization and stromal scarring.[110,119,126,130,140,191] Mehta and coworkers also reported subconjunctival crystals in three patients with PBKC.[119] The origin of these crystals is unknown, although they might contain lipids derived from the meibomian glands.[119] Whether these subconjunctival crystals are underreported in current literature or may only occur in certain ethnicities is still being determined.

5.2.4. Cornea

SPK is the earliest and most frequent corneal manifestation of PBKC and might be prominent during the acute phase of the disease. SPK usually presents focally, but may extend to a diffuse distribution pattern. Punctate erosion may also coalesce, forming epithelial defects in the form of patches, seen most frequently in the interpalpebral zone.[155,190] Corneal vascularization might be present throughout the spectrum of the disease, from pannus formation to severe vascularization associated with corneal infiltrates and ulceration.[71,90,138,155,198] Other common pathologic features include multiple nummular peripheral stromal infiltrates with vascularization. Such lesions are typically gray-white and well-circumscribed, initiating near the limbal zone but invading the paracentral and central areas of the cornea (Figure 4). In severe, chronic, and asymmetric cases, the paracentral and central large infiltrates coalesce, resulting in extensive zones of vascularization, leukoma formation, stromal thinning, and even perforation. Central corneal scarring and leukoma formation finally result in significant visual loss.[110,119,126,130,140,191] (Figure 5)

5.2.5. Face and eyelid skin

Face skin manifestations have been reported in children with PBKC, leading to substantial confusion in the differential diagnosis between ocular rosacea and PBKC. The ocular signs in PBKC and childhood rosacea overlap considerably; however, corneal involvement with irreversible visual loss is rare in childhood rosacea.[10,24,43,53,126,129] Classical findings in PBKC include eyelid hyperemia and telangiectasia on lid margins. The lack of facial skin manifestations in most PBKC patients and the scant long-term follow-up on how many develop rosacea later in life favor the hypothesis that PBKC and childhood rosacea are two different entities.[48,126]

5.3. Risk factors for corneal involvement

The most feared ocular complication of PBKC, without a doubt, is corneal damage. Corneal involvement is the latest stage of the PBKC clinical course.[155] According to the PBKC Study Group Consensus, it is a necessary criterion for the definitive diagnosis of the disease.[126] Several risk factors have been identified in PBKC patients and are related to developing significant corneal damage and consequent vision loss. The main risk factors for corneal involvement include a delay in diagnosis and lack of prompt treatment, female gender, and asymmetric disease.[155] Delay in diagnosis may be attributed to clinicians´ low level of suspicion, lack of access to health systems, and, until recently, a lack of consensus in nomenclature and diagnostic criteria of the disease. A female predominance (up to 87 %) is reported in many studies.[65,71,182,185,191,198] Likewise, Rodriguez-García and coworkers report an association between females and corneal involvement. PBKC is a bilateral but often asymmetrical disease.[155] Interestingly, asymmetric presentation is significantly associated with corneal involvement (OR = 2.77, 95 % CI = 1.12–6.84).[155]

5.4. Refractive changes and induced optical aberrations

PBKC corneal changes induce lower-order aberrations, irregular

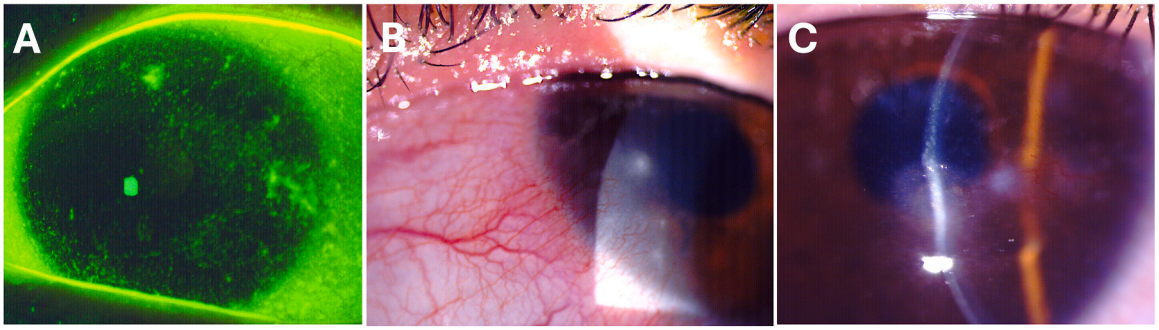


Fig. 4. Pediatric blepharokeratoconjunctivitis acute corneal manifestations. **A.** Intense and diffuse superficial punctate keratitis in active asymmetric PBKC; **B.** Typical multiple peripheral nummular stomal infiltrates with superficial vascularization in the temporal inferior corneal zone; **C.** Paracentral extension of a large stromal infiltrate, showing stromal degradation and thinning.

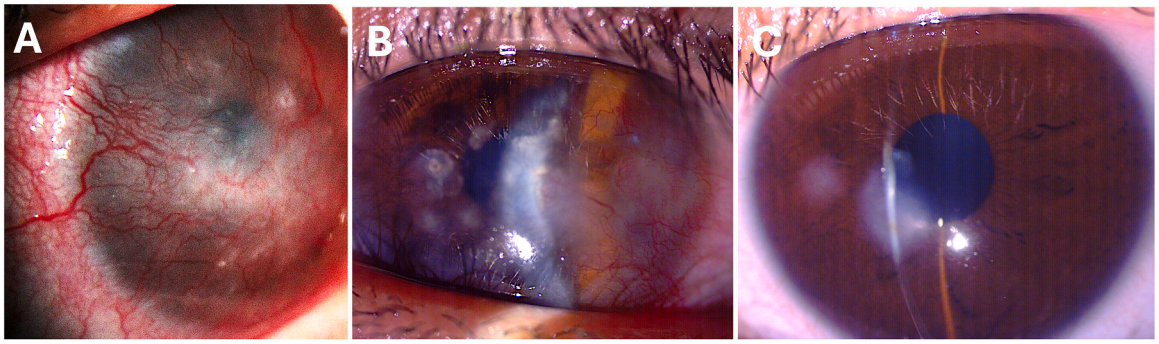


Fig. 5. Pediatric blepharokeratoconjunctivitis chronic corneal manifestations. **A.** Severe invasive corneal vascularization and central stromal infiltration in an adolescent with chronic-recurrent PBKC; **B.** Multiple paracentral and central nummular leukomas affecting the visual axis, accompanied by extensive mid-stromal vascularization and infiltration in a chronic asymmetric PBKC eye; **C.** Paracentral deep stromal scarring and leukomas in a patient with chronic inactive PBKC.

astigmatism, and higher-order aberrations. Limited evidence exists regarding the effect of optical aberrations and visual quality in patients with PBKC. Mendoza-Zamora and coworkers studied the visual impact of higher-order aberrations (HOAs) in PBKC compared to healthy eye controls.[120] In PBKC, the mean induced astigmatism was 1.6 ± 1.98 vs. 0.67 ± 0.76 in the control group ($p = 0.01$). Additionally, there was a significant increase in the total HOAs of PBKC eyes, namely coma, secondary astigmatism, quadrafoil, and pentafoil. Leucoma, corneal vascularization, pannus, and phlyctenule were strongly associated with increased HOAs.[120]

5.5. Visual dysfunction and amblyopia

Corneal opacity/scarring and irregular astigmatism may cause amblyopia in children with PBKC.[117,124] Amblyopia is a visual information processing disorder leading to irreversible vision loss.[76] It may affect one or both eyes resulting from abnormal eye interactions during the critical period of visual cortex development.[16,19,106,200] Causes of amblyopia in PBKC include deprivation by corneal opacities, uncorrected refractive errors that may occur secondary to large chalazion, and irregular astigmatism/corneal aberrations.[120,172] In PBKC, amblyopia is usually diagnosed when vision loss may not be attributed to keratopathy; however, this distinction might be challenging.[87] A widely accepted definition based on vision is a difference of ≥ 2 Snellen or LogMAR lines between eyes.[89,155] The diagnosis of amblyopia in PBKC occurs after inflammation has completely resolved.[125] It may arise from increased irregular astigmatism leading to refractive amblyopia or dense corneal opacities, leading to deprivation amblyopia.[120,125] The latter being the most severe but least common form, accounting for only 3 % of all amblyopia cases.[73]

Unfortunately, up to one-third of patients with PBKC present to the clinic with a visual acuity < 0.3 Log MAR.[87] The reported range of amblyopia goes from 6.14 % to 30 %, depending on the series.[41,65,72,87,90,124] Moon and coworkers defined amblyopia as a best-corrected visual acuity reduction of 0.15 LogMAR or less despite complete resolution of ocular surface inflammation and not attributable to other ocular abnormalities.[124] They report a prevalence of amblyopia of 8.8 % in 137 patients, with increased astigmatism identified as the primary cause.[124] This cohort showed a vast corneal involvement (77.4 %), with 43.1 % presenting corneal scarring.[124] Rodriguez-Garcia and coworkers observed refractive amblyopia in 3.4 % of children without corneal involvement, compared to 7.83 % in the corneal-affected group.[155] Gonzalez-Godinez and coworkers found amblyopia in 6.14 % of patients at any stage of the disease.[65] In their series, the prevalence of amblyopia was 20 % in patients with severe keratopathy.[65.] Jones and coworkers present a striking 30 % prevalence of amblyopia in their entire cohort, escalating to a staggering 88 % in patients with corneal opacities and bilateral corneal involvement at presentation.[87] They also report a mean visual acuity of 0.28 Log MAR at presentation, indicating that a 2-year delay in disease diagnosis led to a 0.06 Log MAR reduction in visual acuity, underscoring the potential for significant visual loss.[87] Moreover, Kaufman and coworkers found similar figures in their cohort of 70 patients (95 eyes) with phlyctenulosis by reporting a 16.8 % rate of amblyopia and 67.4 % of corneal involvement.[90] These findings serve as a reminder of the importance of early diagnosis and treatment in preventing such outcomes. Strategies to avoid it must center on halting disease progression and correcting induced refractive errors. Such conditions underscore the importance of amblyopia intervention in these children, particularly when the PBKC is stabilized, and ocular inflammation is reduced.

5.6. Clinical course and follow-up

PBKC begins as an eyelid margin disease with blepharitis, meibomitis with secondary MGD, and recurrent chalazia (5–79.7 %). Patients with PBKC usually come as a referral with a significant delay in diagnosis.[69,87,126,155] Under such instances, recurring and chronic inflammation usually progresses to corneal involvement and permanent damage.[126] The latter is a typical feature of PBKC; however, few studies have analyzed recurrent inflammation in PBKC. Moon and coworkers analyzed the recurrence patterns of 116 patients, finding 52.6 % reactivation of inflammation with a mean frequency of 1.2 ± 1.7 times (range: 0–10) during a mean follow-up of 1.7 ± 2.4 years (range: 0–14) and a mean time to first recurrence of 33.9 ± 64.3 weeks (range: 0–448 weeks).[125] This underscores the imperative need for further research to identify risk factors for recurrence and improve treatment outcomes. Compliance with eyelid therapy as a maintenance regime and protocolizing treatment in a stepladder approach could improve outcomes and reduce the frequency of reactivation events.[71,137] After a reactivation event is diagnosed, a short-term course of topical corticosteroid and oral and topical antibiotics with anti-inflammatory activity are prescribed *(see Section 8 . Treatment)*. The patient should be monitored closely to assess therapeutic response and potential pressure spikes in steroid responders.[97,133] If remission of inflammation is observed, de-escalation to a maintenance regimen is imperative. In patients without a positive response to therapy, treatment may be escalated to a corticosteroid-sparing regimen with a reassessment every four to six weeks.[135,137,185]

6. Diagnosis

6.1. Diagnostic suspicion and timely diagnosis

PBKC is suspected in a child with a history of recurrent chalazia early in life and acute episodes of red eye, tearing, photophobia, and foreign body sensation, accompanied by eyelid, conjunctival, and corneal signs

of the disease.[126] Early diagnosis of PBKC is crucial to avoid late corneal complications and visual loss. The confusion created by assigning many different names for PBKC in the literature, the lack of a definition, the similarity of symptoms and signs to other ocular surface inflammatory diseases appearing in childhood, and the ambiguous diagnostic criteria for the disease all have contributed to frequent misdiagnosis or late recognition among the ophthalmologic community.[126]

6.2. Diagnostic criteria (PBKC Study Group)

Based on the contributors above-mentioned for PBKC misdiagnosis and late detection, the PBKC Study Group consensus has proposed a definitive diagnosis of PBKC when at least one or more suggestive symptoms (recurrent chalazia, ocular irritation, burning, tearing, chronic discomfort, photophobia, foreign body sensation, blurred vision, and red eyes) accompanied by at least one clinical sign from the lid margin (meibomitis, MGD, inflammation, erythema, chalazion, and hordeola), the conjunctiva (hyperemia, conjunctivitis, and phlyctenules), and the cornea (SPK, phlyctenules, infiltrates, vascularization, pannus, thinning, scarring, and ulcer).[126] In addition, the term PBKC suspect (meets criteria except for corneal signs) was introduced with the aim of a prompt diagnosis and treatment to avoid potential corneal damage. Lastly, skin manifestations (flushing, facial erythema, papules, pustules, and telangiectasia on the forehead, nose, cheeks, and chin) may or may not occur in both definitive PBKC and PBKC-suspect patients.[126]

6.3. Potential diagnostic biomarkers

Although the tear film offers only 5–10 μl available for analysis, it is a highly complex biological mixture of molecules, including proteins, electrolytes, lipids, and metabolites.[210] Analyzing tear biomarkers aids in diagnosis, severity grading, evaluating prognosis and/or monitoring treatment of several ocular surface diseases.[201] The two most common methods for tear film collection are microcapillary tubes, membrane-based supports, and Schirmer-like paper strips, the former being a more practical and less uncomfortable method for children.[39]

Biomarkers associated with inflammatory responses like IL-1α, matrix metalloproteinase (MMP) 9, and MMP-8 were found at higher levels in the tear film of patients with ocular rosacea.[1,12,102,113] Furthermore; extensive research has been conducted on MMP-9 level alterations in patients with dry eye disease, which could be also studied in patients with active PBKC.[104,121]

Other potential tear studies, like glycomic analysis, have shown a high sulfated O-glycan content in tears and saliva from patients with ocular rosacea.[5,139,196] These glycosylation alterations may lead to an abnormal eye and mouth microbiome, favoring specific groups of bacteria.[14,139] Furthermore; when examining meibomian gland secretions in individuals with blepharokeratoconjunctivitis, proteomic analysis revealed the presence of S100A8, S100A9, ANXA3, and LCN2 proteins.[179] These proteins are likely implicated in the chronic ocular surface inflammation observed in blepharokeratoconjunctivitis. So far, no study has described biomarkers for diagnosis, severity, prognosis, or monitoring treatment in children with PBKC.

7. Differential diagnosis

One of the main challenges with diagnosing PBKC is that its signs and symptoms are varied and nonspecific. Moreover, many other ocular surface inflammatory and infectious diseases presenting during childhood and adolescence may clinically resemble PBKC. Of those, childhood rosacea and PKC are often misdiagnosed as PBKC due to the significant overlap in ocular findings;[126] however, the differential diagnosis of PBKC also includes chronic allergic keratoconjunctivitis (vernal and atopic with or without eyelid dermatitis), herpes simplex virus (HSV) infections, adenoviral keratoconjunctivitis, and bacterial conjunctivitis. Other rare disorders may also be confused with PBKC, including Thygeson SPK, *Molluscum contagiosum,* and *Phthirus pubis* lesions around or on the eyelids with conjunctival/corneal indirect toxic reaction.[15,33,34] (Table 2)

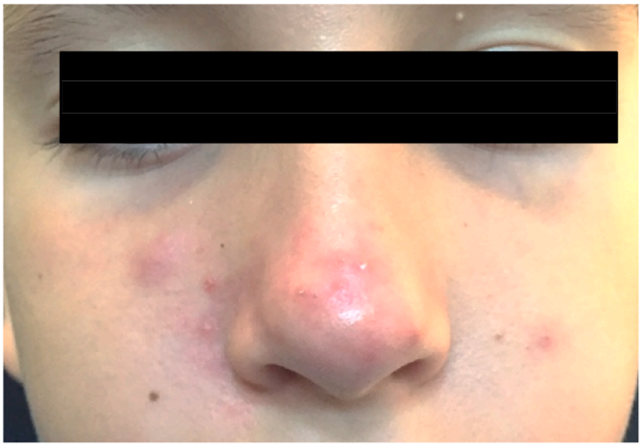
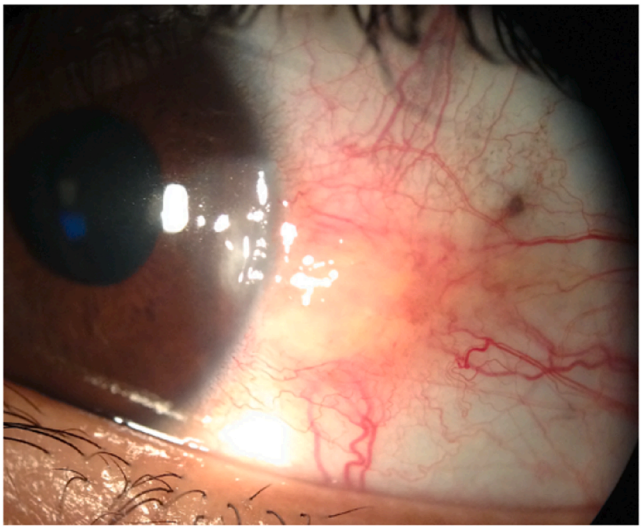
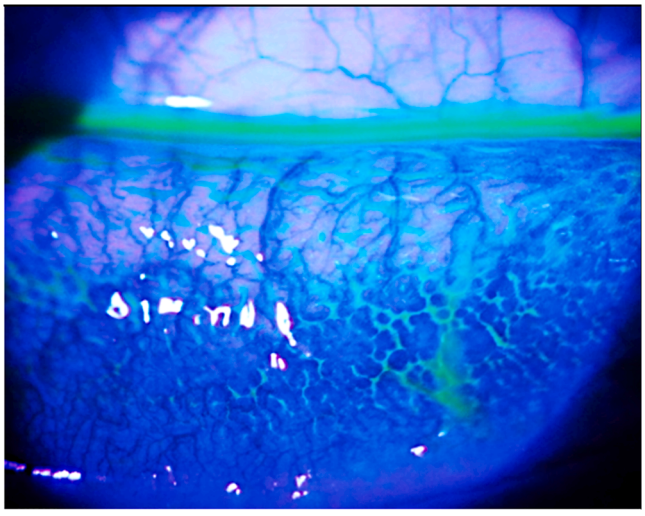
7.1. Childhood ocular rosacea

Childhood ocular rosacea is a chronic inflammatory skin disorder typically seen in Fitzpatrick type 1 or 2 phototypes predominantly affecting the Centro facial region.[2,187] Characterized by persistent facial erythema associated with periodic flushing induced by potential trigger factors (i.e., alcohol and caffeine beverages and hot spicy foods containing capsicum), phymatous changes, telangiectasia, and often papules, and pustules, rosacea typically impacts patients at mature age (between 30 and 59 years old).[154,174,187] Ocular rosacea is the clinical spectrum of ocular manifestations considered subtype 4 rosacea by the National Rosacea Society;[202] however, since rosacea might encompass several signs and symptoms, a recent consensus on the diagnosis focuses on phenotypes rather than the classic subtypes classification.[60,202] The ocular syndrome is characterized by chronic inflammation involving the eyelids and, to a variable extent, the conjunctiva and cornea.[154] Although childhood rosacea is considered a rare disease, this is probably related to underdiagnosis due to this age group's lack of diagnostic criteria.[101] Furthermore, the clinical similarities between pediatric ocular rosacea and PBKC are intriguing. The fact that some patients with PBKC develop dermatological manifestations and the efficacy of anti-inflammatory and antimicrobial therapy in both entities leads us to believe that these entities may share a common step in the pathogenic process; however, PBKC may be present in the complete absence of skin manifestations, has marked epidemiological differences, there is a lack or unknown environmental and dietary triggers, the eventual waning of the inflammatory response during puberty, and the scant follow-up on how many of them develop rosacea later in life lead us to believe that they are different entities.[126]

7.2. Phlyctenular keratoconjunctivitis (PKC)

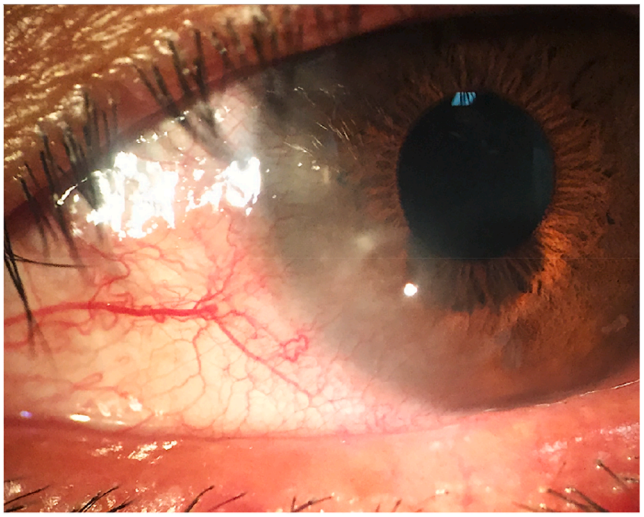
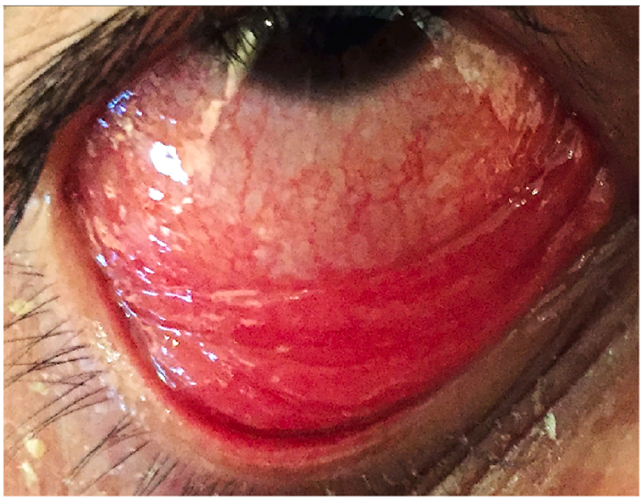
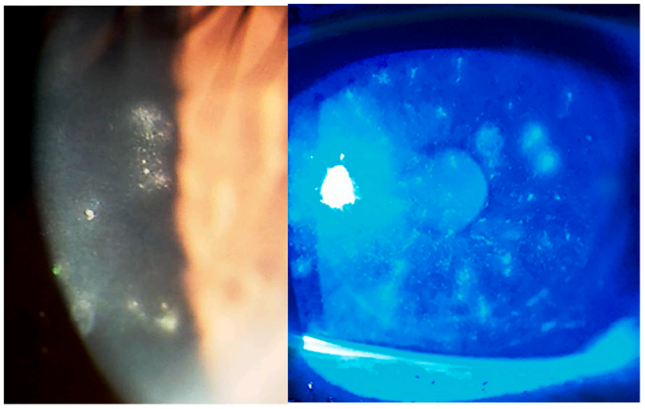
A phlyctenule is a common sign of PBKC and is responsible for confusing terminology with the classic description of PKC.[63,182] PKC is a distinct clinical entity induced by a type-IV Coombs & Gell's hypersensitivity reaction to putative proteins from the cell wall of *Mycobacteria, Staphylococci, Cutibacterium,* and many other bacterial antigens.[180,182,183,185] PKC is characterized by acute and recurrent episodes of nodular inflammation of the conjunctiva and peripheral cornea with or without epithelial defect.[90,138] Although anterior blepharitis with collarette secretions on the lid margin is frequently described, focal Meibomian gland involvement has been less recognized at the lesion site.[90] Kaufman and coworkers found no strong relationship between phlyctenular formation and meibomian gland involvement.[90] In contrast, Suzuki and coworkers described a significant association between the severity of corneal phlyctenules and neovascularization with the severity of meibomitis.[182] This may be attributed to variations in genetic predispositions, environmental factors, or differences in diagnostic criteria between the two populations. Additionally, phlyctenules arise mainly in the conjunctival limbal area of the interpalpebral zone. In severe cases, corneal stromal neovascularization may occur.[182] Contrarily, PBKC phlyctenule formation shows peripheral but significant paracentral and central corneal involvement with prominent vascularization, producing significant visual consequences. Jo and coworkers described 26 PKC patients, of whom 77.1 % showed corneal involvement, with 40.7 % affecting the visual axis. Interestingly, most of the patients were between 11 and 20 years of age at the time of presentation.[84] It could be possible that patients with severe corneal involvement and affected vision in these series had PBKC rather than PKC (Table 2).

Table 2
Main clinical features of the differential diagnoses of pediatric blepharokeratoconjunctivitis.

Disease	Distinguishing clinical features	Clinical appearance
Childhood or pediatric rosacea	Ocular manifestations include recurrent chalazia and conjunctival hyperemia. Corneal changes have rarely been reported in children. Skin manifestations, including facial flushing, erythema, telangiectasia, and/or papules and pustules, and nasal phymatous changes without comedones, are part of the definitive diagnostic criteria. They may occur before ocular manifestations but can appear simultaneously, and even after them, especially in children.	
Phlyctenular keratoconjunctivitis	Acute recurrent nodular inflammation of the meibomian glands, conjunctiva, and peripheral cornea that may or may not ulcerate. Phlyctenules mainly situate in the interpalpebral bulbar conjunctiva or at the limbus but rarely surpass the peripheral cornea; therefore, scarring and neovascularization of the visual axis are unlikely. Corneal nodules and neovascularization correspond with the location and severity of the meibomitis —strong association with *Cutibacterium acnes*.	
Allergic keratoconjunctivitis	Usually presents with red eye, tearing, foreign body sensation, pseudoptosis, and photophobia. Unlike PBKC, there is typically intense ocular pruritus, significant papillary response, and associated respiratory or skin symptoms and signs. Corneal manifestations in allergic eye disease include SPK, shield ulcers, and Horner-Trantas dots	

(*continued on next page*)

Table 2 (*continued*)

Disease	Distinguishing clinical features	Clinical appearance
Herpes simplex keratoconjunctivitis	Unlike PBKC, herpetic disease in the eyelid presents as a vesicular rash and corneal dendritic or geographical epithelial ulcerations with decreased corneal sensitivity. A herpetic limbitis may be difficult to differentiate from PBKC. Moreover, meibomitis is usually absent in herpetic infections, and the disease is typically unilateral.	
Adenoviral keratoconjunctivitis	Acute red eye, watery discharge/tearing, foreign body sensation, and photophobia. Particularly contagious, so often bilateral infection and family relatives or friends with similar ocular manifestations is seen. Interrogation often reveals flu-like symptoms, adenopathy, myalgia, and upper respiratory tract infections.	
Thygeson's superficial punctate keratitis (TSPK)	Rare disorder characterized by episodic red eye, photophobia, tearing, foreign body sensation, and blurred vision resemble active PBKC. In contrast to PBKC, TSPK rarely has palpebral or conjunctival involvement. The typical lesions are elevated or flat, round-oval-shaped, gray-whitish lesion occupying the central intraepithelial cornea with minimal underlying stromal edema or inflammation.	

7.3. Childhood ocular allergy

Comparable to PBKC, children with vernal keratoconjunctivitis (VKC) usually present with red eye, tearing, foreign body sensation, pseudoptosis, and photophobia. Unlike PBKC, there is typically intense ocular pruritus, significant giant papillary response, conjunctival chemosis, and associated respiratory or skin symptoms and signs.[3] Also, VKC manifestations differ from PBKC in specific signs, like lower eyelid skin shiners, corneal shield ulcers, limbal Horner-Trantas dots, and gelatinous limbal conjunctiva hyperplasia.[211]

Eyelid atopic dermatitis or eczematoid blepharitis is another clinical entity that may be confused with PBKC.[3] These children present with pruriginous desquamative epidermal plaques and conjunctival hyperemia. Lichenification, thickened erythematous eyelid skin with marked epidermal folds and fractures, is typically seen after repetitive dermatitis.[3] Other ocular atopic disease-associated manifestations like the Dennie-Morgan double fold on the lower eyelid, the thinning or loss of the outer third of the eyebrow (Hertoghe sign), and the nasal crease

(nasal salute) are not present in PBKC.[3,211] Finally, PBKC and allergic eye disease may coexist, making it a significant diagnostic challenge.

7.4. Herpetic eye disease in the pediatric age

HSV-blepharokeratoconjunctivitis and keratitis may also mimic PBKC, causing corneal stromal infiltration and scarring with vascularization (Table 2). Unlike PBKC, herpetic blepharokeratoconjunctivitis may present as an acute periocular vesicular eyelid skin rash and more commonly with follicular conjunctivitis and typical corneal dendritic or geographical epithelial ulcerations with decreased corneal sensitivity.[110] There is no history of previous eyelid inflammation or recurrent chalazia, meibomitis, or phlyctenules, which are usually absent in herpetic infections, and the disease is primarily unilateral.[110]

7.5. Adenoviral keratoconjunctivitis

Adenoviral keratoconjuctivitis, in the form of pharyngo-conjunctival fever (PCF) or epidemic keratoconjunctivitis (EKC), presents with acute "red, watery eye," foreign body sensation, and photophobia. There is prominent follicular conjunctivitis and marked conjunctival hyperemia (Table 2). The eyelids are usually not involved, and at the late stages of the disease, up to 50 % of cases develop typical scattered multifocal subepithelial infiltrates.[83] Unlike PBKC, adenoviral keratoconjunctivitis may be preceded by flu-like symptoms such as malaise, fever, preauricular adenopathy, myalgias, and respiratory symptoms (PCF). EKC is also particularly contagious, so detailed interrogation often reveals household or daycare outbreaks.[83]

7.6. Acute bacterial blepharoconjunctivitis

Acute bacterial conjunctivitis is characterized by acute, unilateral red eye with increased mucopurulent secretion (green or yellow discharge), sticky eyelids, and foreign body sensation.[20] Other manifestations include itching and early-morning "glued" eyes, which may be associated with systemic infections, particularly otitis media and upper respiratory tract infections.[20] Contrary to PBKC, this disorder is usually not chronic or recurrent and has an excellent prognosis and a high frequency of spontaneous remission.[77]

7.7. Thygeson superficial punctate keratitis (TSPK)

TSPK is a rare clinical entity in which episodic red eye, photophobia, tearing, foreign body sensation, and blurred vision occur, resembling active PBKC.[189] These patients also have a chronic course with exacerbations and remissions. In contrast to PBKC, this entity rarely has palpebral or conjunctival involvement. The characteristic corneal findings include the presence of multiple scattered, whitish-grey, and slightly raised punctate lesions that may or may not stain with fluorescein and no phlyctenule formation. Such lesions are mainly in the intraepithelial zone with minimal or no subepithelial edema (Table 2).[189]

8. Medical treatment strategies

Since PBKC is a chronic condition with frequent exacerbations and the potential for corneal scarring and permanent vision loss, early detection and opportune therapy must be directed to avoid disease

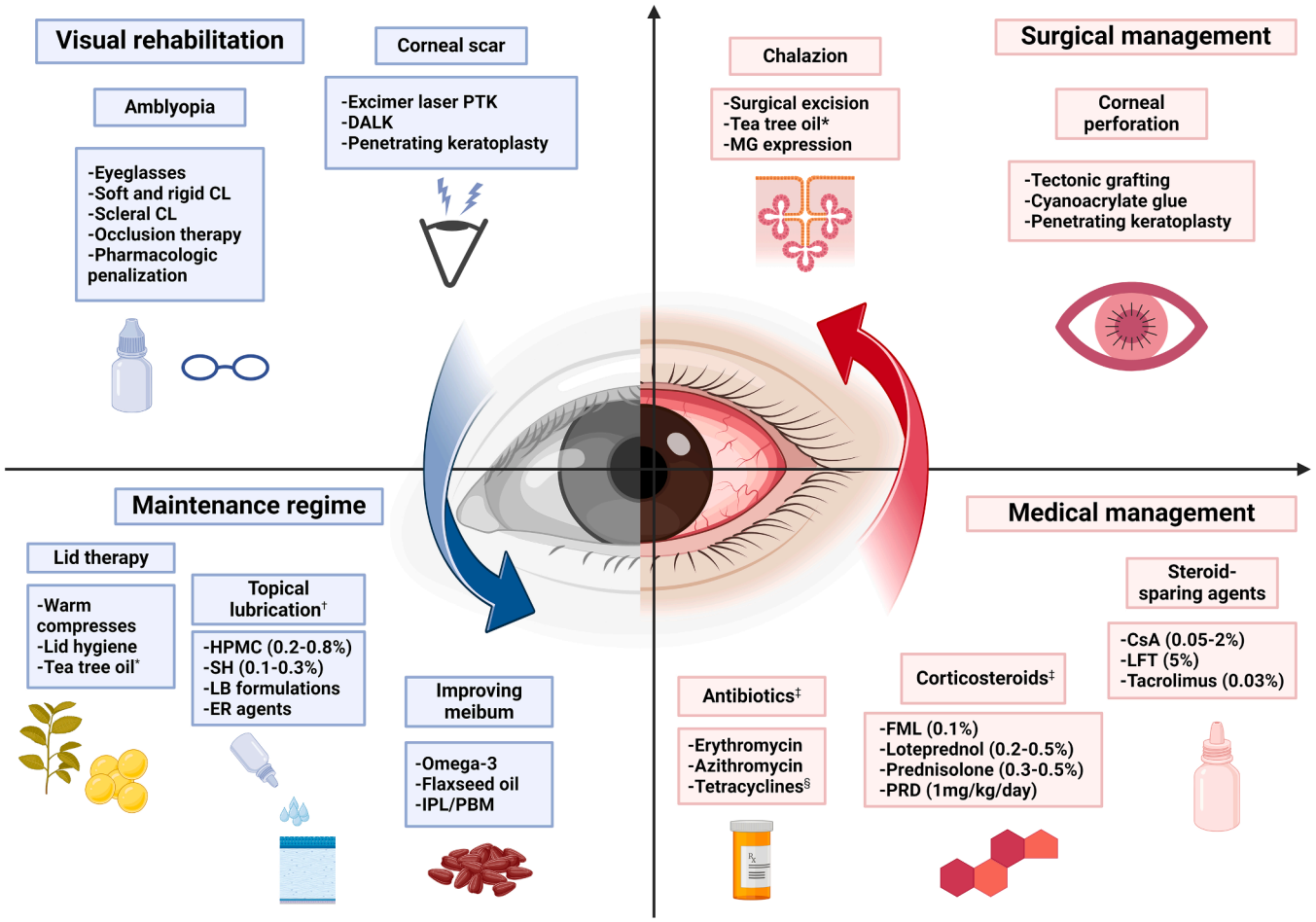


Fig. 6. Main therapeutic alternatives for the management of pediatric blepharokeratoconjunctivitis.

recurrence, control inflammation, improve vision, and manage complications (Figure 6).[71,198] Similar to managing blepharitis and MGD in adults, the treatment of PBKC aims to improve MG function, reduce the bacterial load at the lid margins and conjunctiva, and minimize ocular surface inflammation.[135] Parents play a crucial role in the management of PBKC. Their education regarding the relapsing and remitting course of PBKC is mandatory to ensure follow-up and treatment compliance.[156] To achieve the latter, eye care specialists must understand the potential pathogenic mechanisms (discussed above) underlying PBKC to prescribe appropriate treatment.

8.1. Lid therapy

Lid hygiene represents the cornerstone of PBKC management. The technique for performing hygiene of the eyelids is as follows:[71,128,135,156,158,161]

1. With the eyes closed, warm the eyelids with hot compresses for 5 min. In children, warming one eye at a time while otherwise distracted might enhance patient cooperation. Another alternative is the use of moist heat packs or electric heating goggles.
2. Starting on the medial canthus and finishing on the lateral canthus, apply gentle pressure with the fingertip on the inferior eyelid to express the MG. Repeat the procedure in the superior and inferior eyelid margins of both eyes.
3. Using a cleansing eyelid pad, scrub the four lid margins to remove the anterior border secretions, oily debris, and cylindrical dandruff.

8.2. Repeat the above steps at least once a day

In most cases, this 4-step technique effectively keeps the eyelid margins clear of bacteria and debris in PBKC. In our practice, we actively educate parents and patients, demonstrating and reminding them of the correct lid hygiene technique. This approach has proven successful in establishing confidence in the management of PBKC.

Patients must be evaluated for other ocular comorbidities, including *Demodex* infestation, which may also exacerbate PBKC if not adequately managed.[156] A systematic review by Navel and coworkers reported *Demodex* blepharitis resistant to standard lid hygiene with warm compresses and topical antibiotics.[128] They suggest combining tea tree oil (TTO) with eyelid margin cleansing once or twice daily as a first-line treatment for *Demodex* blepharitis.[128] Eyelash colonization by *Demodex* mites may incite humoral immunity, leading to ocular inflammation and subsequent PBKC exacerbation.[146] TTO decreases interleukin (IL)-1β and IL-17 concentration, reducing ocular surface inflammation and irritation.[161] Patel et al. reported clinical improvement of signs and symptoms in patients with BKC after 3 months of 50 % TTO and 2 doses of oral ivermectin (200 mcg/kg).[146]

8.2.1. Fusidic acid

Fusidic acid has been used since the 1960s to manage staphylococcal infections. Tabbara and coworkers managed 20 cases with staphylococcal keratitis, 15 of which were methicillin-resistant but fusidic acid sensitive, with 1 % fusidic acid 6 times per day.[186] Evidence of healing was documented in 17/20 (85 %) of cases at a mean time of 10.5 (range: 10–21) days.[186] Today, fusidic acid has fallen out of favor in clinical practice, most likely related to the increasing rates of antimicrobial resistance of *S. aureus*.[42]

8.3. Flaxseed oil/Omega-3 supplementation

In a retrospective case series of PBKC patients. Jones et al. reported that a daily dose of 2.5 ml of flaxseed oil effectively prevented disease exacerbations. This was particularly significant in patients whose disease recurred when systemic antibiotics were discontinued.[87] Further randomized controlled trials are needed to determine the efficacy of Omega-3/flax seed supplementation in children with PBKC.

8.4. Potential interventional lid therapy alternatives for patients with PBKC

Electromechanical heating (i.e., LipiFlow®, iLux®, MGDRx®) and lid margin debridement (i.e., BlephEx®) devices, combined or not with intense pulse light (IPL) therapy or photobiomodulation (PBM), are expensive interventional alternatives currently and widely used for chronic blepharitis and MGD, with good results regarding reducing inflammation and improving MG function;[160] however, most safety and efficacy clinical trials have been performed in adults, with little or no evidence of their safety and usefulness in children and adolescents with different forms of chronic blepharitis/MGD and PBKC. Although low-fluence IPL has shown to be a safe and effective alternative to treat moderate-to-severe blepharitis in children, another study has found a high prevalence of post-treatment headaches, and| epidemiologic findings of increased risk of skin cancer in children highly exposed to sunlight have aroused concerns about IPL use in children.[151,209] Therefore, well-designed large RCTs are needed to elucidate the safety and efficacy of these therapeutic alternatives in these age populations, including patients with PBKC.

8.5. Topical lubrication

Lubricant eye drops are necessary for PBKC to address the evaporative dry eye disease (DED) resulting from inflammatory MGD, the hyperosmolarity status of the ocular surface, and, indirectly, its inflammation.[69,135] Chronic DED symptoms are exacerbated by excessive use of digital screen devices at the pediatric age, leading to reduced blinking and increased ocular surface disruption.[156] Ocular lubricants dilute pro-inflammatory tear cytokines concentration and reduce tear hyperosmolarity and the shearing forces created by the tarsal conjunctiva on the ocular surface during blinking.[134,159] To avoid toxic preservative effects (e.g., benzalkonium chloride [BAK]), preservative-free ocular lubricants are preferred in PBKC.[26,86] Patients with severe DED requiring frequent application of ocular lubricants or those requiring concomitant use of other ocular medications (i.e., hypotensive drugs, steroids, antibiotics) should avoid BAK-containing formulations.[26]

Despite tear evaporation constituting the primary pathogenic mechanism of DED in patients with PBKC, concomitant aqueous tear underproduction often coexists.[71,72] Unfortunately, well-controlled RCTs of ocular lubricants for DED management in the pediatric population are currently lacking; however, numerous authors suggest that a similar approach might be used to manage PBKC-associated DED.[69–71,87,135,156]

8.5.1. Hydroxypropyl (HPMC) and carboxy-methylcelluloses (CMC)

HPMC and CMC are well-studied viscoelastic polysaccharides available in multiple concentrations ranging from 0.2 % to 0.8 %.[127,194] A recent Cochrane review reports that HPMC is safe and effective for managing patients with low-to-moderate DED symptoms.[150] On the other hand, CMC has high micro viscosity properties, which allow its retention on the cornea for a prolonged time. An *in vitro* study reported that CMC may remain bound to human corneal epithelial cells for up to 2 hours, giving it a higher retention capacity and healing properties in moderate to severe DED.[61] Both components are safe and effective when applied 3 to 4 times daily.[150]

8.5.2. Sodium hyaluronate (SH)

SH is a high-molecular-weight glycosaminoglycan naturally present in the tear film with excellent hygroscopic properties.[144,159] Due to its viscoelastic rheology, SH is a highly moisturizing ocular lubricant with a higher residence time than other artificial tears that facilitate wound healing.[114] An RCT demonstrated that 0.1 %, 0.15 %, and 0.3 % SH eyedrops administered 4–6 times per day were equally effective in improving the signs and symptoms of tear deficient and evaporative dry eye patients.[144]

8.5.3. Lipid-based formulations

Lipid= based formulations are safe and effective in the management of evaporative DED.[63] Holly and Lemp first described that water required a low surface tension and a high surface adhesiveness to spread over a surface.[75] Vicario-de-la-Torre and coworkers developed an artificial tear formulation composed of SH, a mucin that enhances adhesion, and phospholipid (phosphatidylcholine and cholesterol)- and vitamin E-based liposomes to reduce surface tension.[195] The authors reported that the liposomal formulations' pH (range: 7.47–7.45), osmolarity (194–201 mOsm/L), surface tension (35.0–37.7 mN/m), and viscosity (2.95–3.11 mPa*s) remained stable for 8 weeks when stored at 4°C. The formulation showed good *in-vitro* and *in-vivo* tolerance.[195] Vigo and colleagues compared the safety and efficacy of Trimix (Off Health Italia, Italy), a formulation composed of trehalose, hyaluronic acid, and cationic liposomes, including phospholipids and stearyl amine *versus* placebo on DED patients.[197] After 2 months of 3 daily therapies, the noninvasive TBUT, tear meniscus height, and lipid-layer thickness significantly increased in the experimental group.[197] The cationic liposomes contained in these formulations provide the polar and nonpolar lipids that reload the lipid layer of the tear film, thus increasing its thickness. Moreover, the electrostatic forces generated between water exposed to these positively charged moieties and the negatively charged proteins of the aqueous layer of the tear film further stabilize the lipid layer.[35,204]

McCann and coworkers compared the efficacy of 0.15 % SH, 0.3 % HPMC, and oil-in-water emulsion eyedrops instilled four times daily for 3 months in patients with evaporative DED.[114] They report a significant reduction in evaporation and an improvement in symptoms in all groups; however, a significant decrease in corneal staining and osmolarity was observed only in the emulsion group.[114] Miháltz and coworkers performed an RCT evaluating the effect of 0.2 % SH versus lipid-based eyedrops administered at least 4 times daily on ocular surface parameters and optical quality in patients with MGD.[122] After 3 months, both groups observed significant improvement in tear breakup time, symptoms score, and ocular surface staining. Nevertheless, patients with severe MG dropout (>50 %) managed with lipid-based drops experienced significantly greater improvement in the optical quality and high-order aberrations compared with the SH group.[122]

8.5.4. Epithelial restoration agents

Epithelial restoration agents, including 3 % trehalose and 5 % dexpanthenol, effectively restore the corneal epithelium. Trehalose is a nonreducing disaccharide crucial in anhydrobiosis (the capability of surviving to almost complete desiccation).[25] Trehalose stabilizes the phospholipids in the cell membrane, thus aids them in preserving their functional properties and cellular contents. It also protects cellular proteins from apoptosis by halting their denaturation under cold, heat, and osmotic stress, oxidant injury, dehydration, and desiccation.[111] Trehalose 3 % has proved its protective effect on desiccated corneal epithelial cells from murine models that underwent corneal epithelium alcohol delamination and low-humidity airflow environment.[6] On the other hand, dexpanthenol is the alcohol form of vitamin B5 (pantothenic acid). It has been used as lubricant/moisturizer for wound healing in dermatology and epithelial regeneration in ophthalmology.[162] Sabur and Acar evaluated the effects of dexpanthenol 2 %/SH 0.15 % eyedrops on corneal epithelial wound healing in patients undergoing corneal cross-linking for managing keratoconus.[162] The treatment was safe and effective for epithelial healing, promoting faster regeneration, keratocyte repopulation, and reduced corneal edema compared to SH only;[162] however, despite their promising effects on the protection and regeneration of the ocular surface, trehalose and dexpanthenol have not been formally studied in children with PBKC.

8.6. Regional and topical antibiotics

Topical antibiotics with antiinflammatory properties are required in patients with blepharitis-related acute infection of the lids to reduce colonization.[34] On the other hand, patients with active disease or keratitis should be treated with prolonged low-dose oral antibiotics to decrease the cellular infiltration in the cornea and prevent neovascularization.[34] Macrolides are the most widely used antibiotics in PBKC.[134,135] Depending on the drug concentration, the bacterial species, and the organism's growth phase, the macrolides' effect may be bacteriostatic or bactericidal.[93] *Staphylococcus aureus*, coagulase-negative *Staphylococcus spp* (*Staphylococcus epidermidis*), and *C. acnes* are frequently cultured microorganisms from the eyelid and conjunctival swabs of PBKC patients. In a systematic review analyzing the role of inflammatory MGD/meibomitis in ocular surface inflammation, Suzuki and coworkers reported that systemic antimicrobial treatment with antibiotics was effective in PBKC.[185] Thus, antibiotics with adequate spectrum activity against such organisms are required.[38,63,180,183]

8.6.1. Topical antibiotics

8.6.1.1. Erythromycin. Topical 0.5 % erythromycin ointment can be safely used as monotherapy twice daily or at nighttime in children with mild PBKC for several weeks to months, depending on the severity of the case; however, their use is mostly combined with systemic antibiotics (See Section 8.5).[34,135,137] Erythromycin ointment applied to a clean lid margin at bedtime may decrease the bacterial load of staphylococcal species and other microflora.[156]

8.6.1.2. Azithromycin (AZT). The use of topical AZT significantly decreased corneal leukocyte infiltration and reduced the expression of IL-1β, intercellular adhesion molecule-1 (ICAM-1), and TNF-α in a murine model of corneal inflammation.[243] A case-control study of impression cytology samples from the eyelid margin and inferior bulbar conjunctiva of patients with posterior blepharitis and MGD, using q-PCR (IL-1β, IL-8, TGF-β1) and an activity assay (MMP-9) found that topical 1 % AZT suppresses the expression of proinflammatory mediators (IL-1β, IL-8, and MMP-9) and increases the expression of TGF-β1 (anti-inflammatory activity).[243,290] Doan and coworkers reported that 1.5 % AZT eyedrops administered twice a day for a median of 6 months (range 4–10) were effective in controlling bulbar hyperemia, conjunctival phlyctenules, corneal inflammation, and blepharitis in childhood ocular rosacea with phlyctenular blepharokeratoconjunctivitis unresponsive to lid hygiene and intermittent topical steroids. No recurrent inflammation was observed after 11 months off treatment.[54]

8.7. Systemic antibiotics with anti-inflammatory properties

8.7.1. Macrolides

8.7.1.1. Erythromycin. The recommended erythromycin dose for managing PBKC ranges from 12.5 to 40 mg/kg body weight or 500–660 mg/day, administered 2 or 3 times daily.[216] Ideally, oral erythromycin should be reduced to the lowest dose needed to control ocular inflammation. Rodriguez-Garcia and coworkers administered systemic erythromycin at low doses (125 mg every other day) for 6–8 months to patients with PBKC, significantly reducing disease recurrence.[236] Gastrointestinal upset and allergic reactions are inconvenient conditions associated with oral erythromycin.[215]

8.7.1.2. Azithromycin (AZT). AZT given a 5 mg/kg/day dose for 4–6 weeks and then titrated according to clinical response, combined with topical anti-inflammatory therapy, has shown to control recurrent PBKC unresponsive to topical antibiotics.[28] Although its mechanism of action is similar to erythromycin, AZT has improved oral bioavailability, higher tissue concentration, fewer gastrointestinal adverse effects, and a longer half-life, allowing a single daily dose; however, it is considerably more expensive than erythromycin.[28] Apart from its bacteriostatic

activity against gram-positive cocci, oral AZT has anti-inflammatory properties, reducing the production of proinflammatory mediators (TNFα, IL-1β), chemokines, and metalloproteinases (MMP-1, MMP-3, and MMP-9).[66,79]

8.7.2. Tetracyclines at a young age

Tetracyclines are used in MGD due to their antiinflammatory rather than antimicrobial properties by inhibiting phospholipase A2, MMPs, and proinflammatory ILs;[63] however, their adverse effect profile, which includes phototoxicity, esophageal irritation, and tooth enamel discoloration, precludes their use in patients under 9–12 years.[86,87]

Tetracyclines bind to cations, forming tetracycline-calcium complexes that deposit in developing bones and teeth, with doxycycline potentially having the lowest incidence owing to lesser affinity for calcium binding.[188] Jones and coworkers safely prescribed doxycycline (100 mg/day) to a 12-year-old girl with PBKC.[87] A recent study reviewing the available evidence on the safety of doxycycline for young children and pregnant or breastfeeding women suggests that the arguments in favor of its use, mainly related to its less avidly calcium-binding effect compared to its tetracycline predecessors, may be incorrect or at least premature.[206] Current American Academy of Pediatrics recommendations endorse using doxycycline for short durations (<21 days) without regard for the patient's age.[178] Doxycycline dosages range from 1 mg/kg/d in neonates to 5 mg/kg/d, with durations generally < 21 days.[178]

8.7.3. Other antibiotics

Systemic amoxicillin with clavulanic acid,[22] topical 0.5 % chloramphenicol,[69] ciprofloxacin, and gentamicin have also been used in PBKC.[87] Amoxicillin 400 mg/ clavulanic acid 57 mg given twice daily for 1 month on average was safe and effective in managing 7 patients with recurrent PBKC.[22]

8.8. Anti-inflammatory drugs, immunosuppressants and immunomodulators agents

8.8.1. Topical corticosteroids

are required in the acute phase of the disease to control corneal inflammation and avoid neovascularization and scarring.[156] Moderate-potency surface formulations, including loteprednol etabonate 0.2–0.5 % or fluorometholone phosphate 0.1 %, are preferred in PBKC to reduce the risk of ocular hypertension, secondary glaucoma, and cataract formation.[156] Hammersmith suggests quick tapering of topical corticosteroids from frequent dosing and slow tapering during infrequent dosing to avoid side effects.[71] A once or twice-weekly prolonged administration of topical corticosteroids may be required in some instances to maintain the control of inflammation.[71,156] Viswalingam and coworkers prescribed either 0.3 %–0.5 % prednisolone or 0.1 % fluorometholone 4 times a day for 4–6 weeks, then tapering to once or twice a day for 2–3 months or longer to control the corneal and conjunctival inflammation in PBKC patients aged 5.4 years.[198] They reported that topical corticosteroids, lid hygiene, and topical or oral antibiotics were safe and effective in controlling the disease, with few recurrences reported after the age of 8 years.[198] It is desirable to closely monitor intraocular pressure in children using topical corticosteroids since they may develop a drastic ocular-hypertensive response.[97,133] Given the progression from OHT to glaucoma, careful monitoring is imperative in patients receiving prolonged or high-potency steroids.[133] Loteprednol etabonate has a well-known safety profile for long-term use in children, avoiding IOP spikes.[29] Moreover, in steroid IOP responders, loteprednol has a lower propensity than prednisolone acetate to increase intraocular pressure. This property may be related to its lower levels in the aqueous humor and, hence, the trabecular meshwork.[132] Also, although loteprednol has a chemical structure similar to prednisolone, it lacks the ketone group at position 20, which is associated with cataract formation;[103] however, no clinical studies compare the outcomes and/or safety profiles of loteprednol, FML, and prednisolone in children.

8.8.2. Cyclosporine A (CsA)

CzA is a calcineurin inhibitor inhibiting T-lymphocyte activation and cloning by blocking IL-2 production. It is used as a steroid-sparing agent.[86] Dahlman-Noor and coworkers recently reported the outcomes of 145 patients with PBKC managed with topical CsA.[32] After initiating CsA 1 mg/ml at a median prescribed dose twice daily, 99 % of cases were able to reduce, and 90 % discontinued topical corticosteroids. Besides stinging (4 cases, 2.8 %) at instillation, no severe ocular or systemic side effects were reported.[32] CsA is FDA-approved for dry eye disease, and no randomized clinical trials are analyzing the efficacy of CsA in PBKC. Also, the benefits of CSA begin after 4 weeks of treatment, and therapy of at least 3 months is advisable.[98]

8.8.3. Tacrolimus 0.03 %

is a calcineurin inhibitor that suppresses T-cell proliferation by binding to FK506 binding protein (FKBP).[192] It is reported to be 100 times more potent than CsA.[11] Tacrolimus ointment 0.03 % (Protopic®) is FDA-approved for treating children with moderate to severe atopic dermatitis; however, it has been used off-label in childhood ocular conditions, such as VKC and PKC.[74,99,163,208] The recommended dose is twice daily. Kymionis and coworkers reported 2 cases of childhood PKC refractory to topical steroids with improvement in the first week of treatment.[99] Yoon and coworkers used tacrolimus to obtain long-term remission in patients with recurrent steroid-dependent PKC.[208] There are no specific case reports of tacrolimus ointment for PBKC, although Joseph and coworkers reported successful use of tacrolimus in two cases with BKC.[88,208]

8.8.4. Systemic immunosuppression

is usually reserved for severe PBKC, including central, unresponsive, sight-threatening keratitis.[33,191] A Delphi consensus on the management of PBKC suggests a short course of oral prednisone (1 mg/kg/body weight), followed by azathioprine or mycophenolate mofetil, is preferred initially.[33] The latter since steroid-sparing immunosuppressants typically require 3 months to achieve full effect.[69] In a small cohort of 10 children with PBKC, 3 (6 eyes) required systemic immunosuppression due to refractory disease.[69] After 3 months, remission was achieved using azathioprine (100 mg/day) and prednisone (initial dose of 60 mg and taper over 4 weeks, 1 patient), azathioprine alone (3 mg/kg/day, one patient), and mycophenolate mofetil (1.5 g/day, 1 patient).[69]

8.9. Visual and amblyopia rehabilitation strategies

Visual and amblyopia rehabilitation strategies are of paramount importance to long-term visual functionality.[156] While visual function is restored with eyeglasses or contact lenses, amblyopia requires patching or penalization.

8.9.1. Eyeglasses

Addressing refractive errors with glasses is the first step in treating amblyopia.[142] Asper and coworkers reported findings in their meta-analysis that support the effectiveness of refractive adaptation in treating amblyopia.[8] In PBKC, regular meticulous cycloplegic refraction is essential, and adjustments to spectacles may be required as the corneal condition changes.[117]

To avoid frequent prescription changes and reduce the economic burden on patients, glasses should be prescribed once the corneal disease is inactive.

8.9.2. Soft contact lenses (SCL) and rigid gas-permeable lenses (RGP-CL)

SCL and RGP-CL effectively treat children's irregular astigmatism and corneal scarring.[85] While SCL are easy to use and thus suitable for PBKC patients with large ametropias and anisometropias, RGP-CL are

ideal for patients with irregular astigmatism that cannot be addressed with SCL.[157] Jone-Jordan and coworkers concluded that patients between 8 and 11 years could wear both types of contact lenses, although the likelihood of long-term adaptation to SCL wear is higher than RGP-CL.[85]

8.9.3. Scleral contact lenses (ScCL)

ScCL represent an alternative for PBKC patients with residual high refractive error, irregular astigmatism, or corneal surface irregularities that are uncorrectable with SCL and RGP-CL.[157,169] ScCLs provide the lens and cornea with a continuous aqueous reservoir between them, protecting the corneal surface and preventing dehydration from exposure to air and the friction associated with blinking, performing as a PROSE (prosthetic replacement of the ocular surface environment) device.[81] Severinsky and coworkers reports that 2 out of the 3 PBKC cases in their cohort were successfully fitted with ScCL with a 12-month follow-up.[169] While ScCL benefit pediatric patients, addressing visual rehabilitation and protecting the ocular surface, their fitting presents challenges, requiring time and patience from both parents and clinicians.

8.9.4. Occlusion therapy and pharmacologic penalization

The primary method for amblyopia treatment is occluding the sound eye to improve the amblyopic eye's visual acuity.[19] According to the Pediatric Eye Disease Investigator Group (PEDIG), moderate (Snellen 20/40–20/80) and severe (Snellen 20/100–20/400) require patching of the dominant eye for 2 and 6 h per day, respectively.[152] Patching is usually initiated after corneal inflammation has been managed and refractive correction has been provided. Delaying treatment may compromise these childrens visual potential.

The application of 1 % atropine eye drops for penalization induces cycloplegia in the non-amblyopic eye, making it a viable option for hyperopic children who do not exhibit improvement with spectacles alone or after using occlusion therapy.[143] PEDIG studies demonstrated comparable outcomes between atropine and eye patching for children aged 3–15 with moderate amblyopia.[147,148,165] Some success has been shown with the use of atropine for severe amblyopia.[153]

8.10. Patient education and counseling

In PBKC, treatment success relies on follow-up and ensuring patients and parents adhere to therapy recommendations. Implementing comprehensible information about the condition, potential risks, and treatment benefits can enhance understanding. Visual materials like infographics and educational videos are suggested to facilitate comprehension (Figure 7). Moreover, sharing testimonials from other parents who have effectively managed the condition can be influential in highlighting positive outcomes achieved through treatment adherence. Raising awareness about the potential consequences of non-adherence, such as the risk of developing amblyopia, can motivate proactive measures in managing the condition. These strategies aim to reduce the loss of therapeutic adherence and encourage active participation in treatment. The final goal is to improve ocular health outcomes for pediatric patients affected by PBKC.

9. Surgical strategies

9.1. Chalazion removal

9.1.1. Indications

Although usually amenable to medical therapy, surgical management is needed in significant and persistent eyelid-deformation chalazion or when visual axis obstruction occurs. Khurana and coworkers compared incision and curettage (I&C) and intralesional steroids in patients with small (1–4 mm), medium (5–7 mm), and large (8–12 mm) chalazia.[91] The resolution rates between I&C and intralesional steroids were 90 % vs. 70 %, 88 % vs. 50 %, and 100 vs. 0 %, respectively. The latter suggests that the size of the chalazia could be a proxy for deciding the treatment approach.[91]

9.1.2. Avoidance strategies

In a case-control study of non-immunocompromised pediatric patients with chalazia, Liang et al. reported that ocular demodicosis, mainly caused by *D. brevis*, was significantly prevalent (70.2 % vs. 13.3 %, $p < 0.001$).[108] Moreover, patients with demodicosis had a higher risk of recurrent chalazia (33.3 % vs. 10.3 %, $p = 0.02$).[108] In these patients, eyelid scrubs or massage with 50 % TTO represents an effective treatment alternative for managing *Demodex* blepharitis and thus prevents chalazia development.[109]

9.2. Corneal tectonic grafting

Tectonic grafting represents an emergency after corneal perforation. Pant and coworkers reported 2 cases of corneal perforation associated with PBKC that were successfully managed with tectonic keratoplasty using a small incision lenticule extraction (SMILE).[141] The immediate postoperative management of both patients included topical antibiotics and corticosteroids; however, both patients were prescribed lid hygiene, daily warm compresses, and TTO for disease control and to reduce the risk of graft rejection. The visual acuity and corneal thickness at the perforation site in these patients were 20/60 and 20/40 and 0.2 and 0.45 mm at 4 and 12 months postoperative, respectively.[141]

Fu and coworkers reported another case of a 14-year-old boy with a corneal perforation associated with PBKC that was managed with cyanoacrylate glue.[59] Due to recurrent leakage, the patient was managed with a multilayered amniotic membrane patch graft (AMT), a sutured amniotic membrane overlay, and a dry matrix amniotic membrane; however, after absorption of the amniotic membranes 6 weeks later, a persistent full-thickness defect was successfully managed with a tectonic mini-Descemet stripping endothelial keratoplasty (mini-DSEK). The visual acuity was 20/30 at 8 months postoperative.[59]

9.3. Deep anterior lamellar keratoplasty (DALK)

DALK is a safe and effective procedure for managing pediatric corneal pathologies, including keratoconus, microbial keratitis, corneal scar, and PBKC.

Elbaz and coworkers evaluated the structural and visual outcomes of the layer-by-layer DALK technique in 42 children, including 9 (18 %) with PBKC.[50] Among the latter, 2 (22 %, mean time 18.2 months) eyes developed graft rejection and 1 (11 %, mean time 4.8 months) graft failure. A repeat DALK was successfully performed in the child who developed graft failure 1 year after the first procedure. The visual acuity at the last visit ranged from Snellen 20/40–20/70. The authors concluded that layer-by-layer DALK, avoiding the ABB technique, is safe in the pediatric population; however, visual outcomes were suboptimal, primarily due to amblyopia.[50]

9.4. Penetrating keratoplasty (PKP)

Deep corneal scarring with ulceration and perforation is the most severe complication of PBKC.[69] Although PKP is safe and effective in children, postoperative complications and the higher risk of graft rejection and secondary failure favor the use of DALK when possible.[7] (Figure 8) Medsinge and coworkers reported the case of a 12-year-old girl with acne rosacea and MGD with a history of bilateral pannus, right eye corneal perforation, and left eye corneal stromal abscess.[117] Due to tissue unavailability, the patient was managed stepwise with a double-layered AMT followed by a PKP in the right eye. After an episode of epithelial rejection (at 1 month postoperative), endothelial rejection (at three months), and herpetic keratitis (at 12 months) with secondary cataract development managed with topical steroids, systemic steroids,

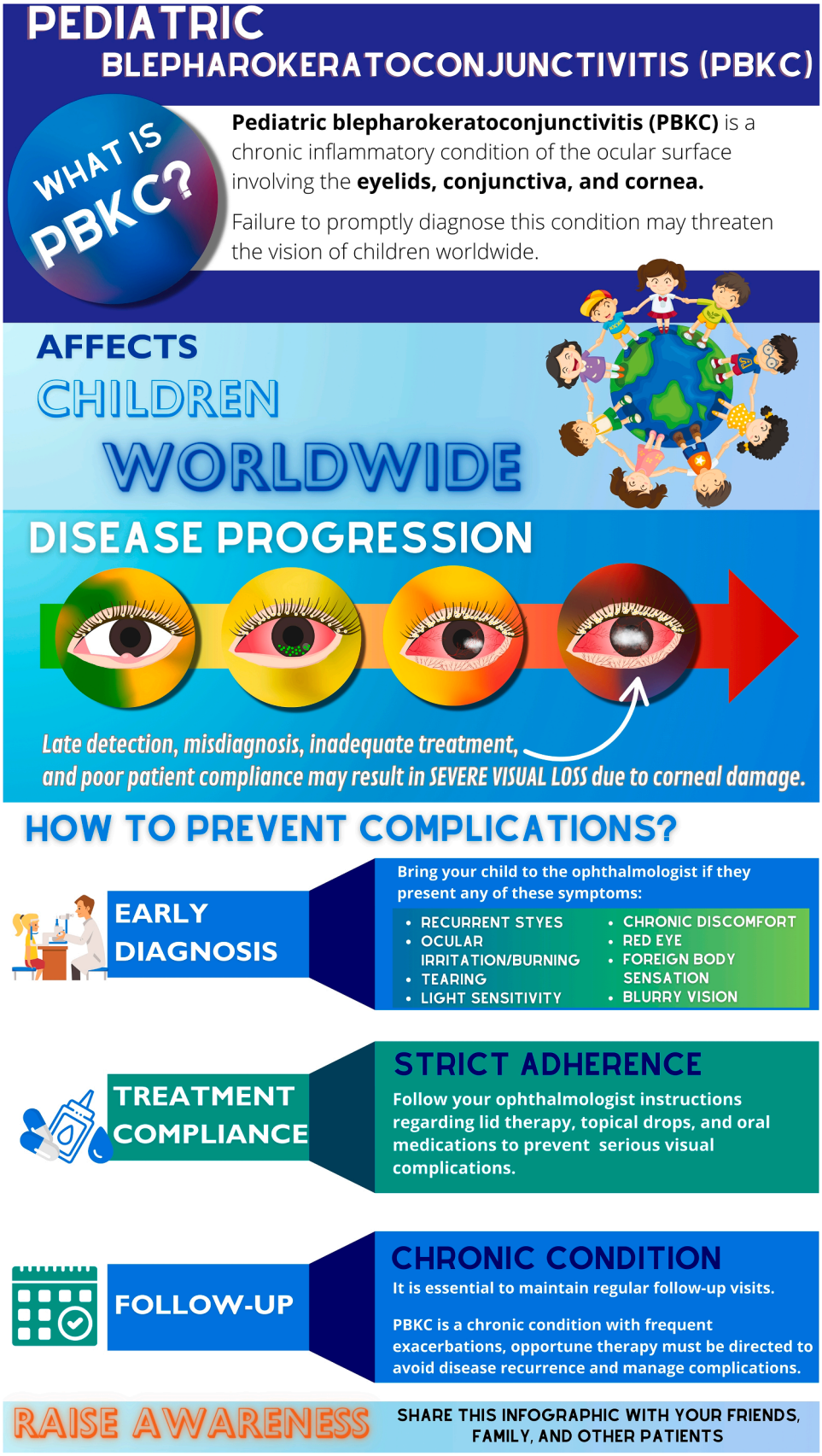


Fig. 7. Educational iconographic representation of the importance of close follow-up and therapeutic compliance for patients and parents (tutors) in pediatric blepharokeratoconjunctivitis.

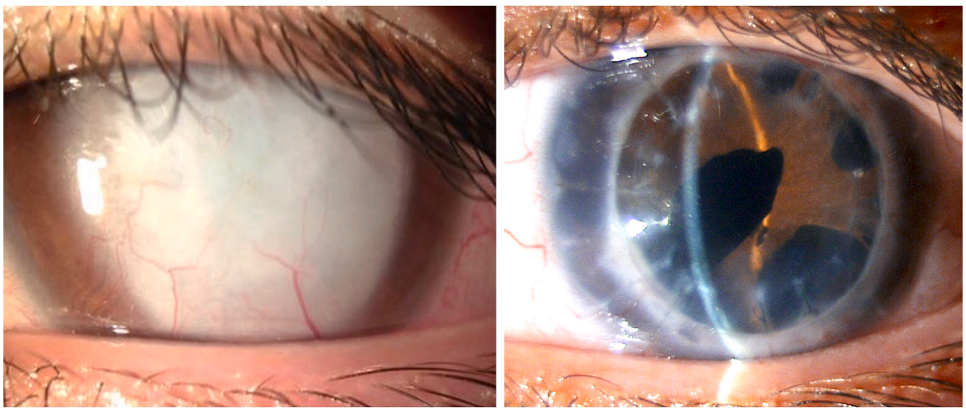


Fig. 8. Penetrating keratoplasty for visual rehabilitation in PBKC. **A.** Extensive central corneal scarring and vascularization after multiple recurrent episodes of inflammation and perforation in the left cornea of a 14 old-year-old girl with asymmetric PBKC and secondary glaucoma; **B.** Four-year follow up postoperative image of a clear corneal graft (CDVA 20/60 Snellen) after a triple procedure (PKP + Cataract extraction and PC-IOL implantation) showing peripheral secondary polycoria due to previous extensive peripheral anterior synechiae.

and tacrolimus, and acyclovir with lensectomy and intraocular lens implantation, respectively, the patient attained a 6/9 visual acuity at 5-year follow-up.[117]

Follow-up after corneal surgery for PBKC should include a meticulous exam to detect early eyelid margin inflammation. Moon and coworkers reported a 52.6 % reactivation of inflammation during a mean follow-up of 1.7 ± 2.4 years (range: 0–14).[125] Early detection and timely treatment of eyelid inflammation will help us maintain good long-term surgical outcomes.

10. Conclusions

PBKC is a severe cause of ocular morbidity in children, necessitating early clinical suspicion and awareness to prevent misdiagnosis and delays in treatment. Unified terminology, definitions, and diagnostic criteria proposed by the PBKC Study Group aim to facilitate accurate detection and prompt management. Effective control of inflammation and reduction of the ocular surface's bacterial burden using antibiotics and antiinflammatory therapies are pivotal in active disease management, with lid hygiene and ocular surface lubrication as essential maintenance strategies. Concurrently, addressing refractive errors and amblyopia through eyeglasses and patching or penalization is critical to ensuring optimal long-term visual outcomes. Future research should focus on conducting high-quality RCTs to standardize clinical care and therapeutic approaches alongside basic and translational research to elucidate the pathogenic mechanisms of PBKC. These efforts will enable the development of novel, targeted therapies to enhance outcomes for affected children.

11. Methods of literature search

We searched the National Library of Medicine's PubMed, Google Scholar, and Scopus databases for articles in English published from inception up to January 2023. Search terms used included "pediatric blepharokeratoconjunctivitis," "childhood ocular rosacea," "childhood blepharokeratoconjunctivitis," "blepharoconjunctivitis," "meibomitis-related blepharokeratoconjunctivitis" and "staphylococcal blepharoconjunctivitis." Abstracts were screened for relevance, and references were cross-checked for relevant publications.

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CRediT authorship contribution statement

Alejandro Rodriguez-Garcia: Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **J. Homar Paez-Garza:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Data curation. **Nallely R. Morales-Mancillas:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Data curation. **Raul E. Ruiz-Lozano:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Gustavo Ortiz-Morales:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation.

Declaration of Competing Interest

No conflict of interest declared.

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