Chapter

Bacterial Keratitis

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Abstract

Bacterial keratitis is a disease prevalent in the underdeveloped and developing worlds and is a significant cause of vision-threatening keratitis across the globe. Early and exact diagnosis, accurate treatment, and regular follow-up are key determinants of success in these cases and allow to prevent serious complications and ensure optimal patient outcomes. This chapter provides a comprehensive overview of the causes, symptoms, diagnosis, and management of bacterial keratitis. The importance of accurate diagnosis based on culture of corneal scraping, and smear examinations, as well as with the use of diagnostic tools, such as confocal microscopy is highlighted. Treatment options, including medical treatment and surgical interventions, are discussed in detail. Moreover, the chapter provides insights into the latest research and developments including new treatments. It also highlights the need for ongoing monitoring, regular follow-up, and good compliance between patient and doctor to ensure optimal patient outcomes. The patient must be educated to avoid risk factors. The superficial ulcer usually responds well to medical management, whereas deeper non-resolving ulcers require therapeutic penetrating keratoplasty for globe salvage. Overall, this chapter serves as an important resource for clinicians, researchers, and healthcare professionals, providing valuable information on the diagnosis and management of bacterial keratitis.

Keywords: bacterial keratitis, bacterial corneal ulcer, corneal infection, infectious keratitis, medical therapy

1. Introduction

Infectious keratitis (IK) is a condition that can occur as a consequence of pathogen invasion into the tissue or as an autoimmune disease accompanying systemic diseases. IK is a corneal infection also known as corneal opacity or corneal ulcer. IK represents the fifth leading cause of blindness globally, accounting for ~3.2% of all cases [1]. It is estimated to be responsible for 1.5–2.0 million cases of unilateral blindness annually [2]. According to WHO, 1.9 million people have corneal blindness due to the opacification of the cornea, which accounts for about 5% of the total patients who have blindness [3]. Corneal Opacity accounts for 3.46% of global blindness and 1.65% of global blindness and visual impairment. Infectious keratitis can be divided into microbial keratitis, including bacteria, fungi, or parasites and viral keratitis, including herpes viruses [4]. Microbial keratitis is an infectious disease of the eye, in which the cornea is inflamed. Bacteria are most concerning due to rapidly progressive vision-threatening keratitis with irreversible visual sequelae. The localization of corneal inflammation is important, and acute inflammations usually affect the central part of the tissue,

while peripherally located forms of corneal inflammation are more often of prolonged inflammation with an etiology that is difficult to clearly determine.

Bacterial keratitis (BK) is the most common type among all types of infectious keratitis. BK accounts for approximately 65–90% of all microbial keratitis [5]. BK rarely occurs in the healthy eye because of the human cornea's natural anatomical barrier to infection. BK is caused by varied bacterial species, and it can be an acute, chronic, or transient infectious process of the cornea. BK is one of the most common causes of visual impairment in working-age adults. BK is one of the most serious ocular infections, and it can progress rapidly and may lead to serious complications including vision-threatening keratitis. Acute keratitis may progress with tissue necrosis and its perforation within even several dozen hours. When analyzing the causes of bacterial keratitis, a number of external factors should be taken into consideration such as climate, geographical zone, level of hygiene, patient's workplace, use of contact lenses, and the endemic occurrence of various eye diseases. Whereas local factors include medical history, especially dry eye syndrome, other local disorders of the eye surface, especially those affecting the epithelium and the human margin, surgical procedures, or the presence of sutures. The diagnosis of BK is based on clinical and microbiological evaluation. Thus, to avoid a serious complication early and immediate medical treatment is needed. Recently, in the past few decades have seen increasing contact lens users, resulting in proportionately increased of bacterial keratitis and corneal ulcers [6].

2. Etiology

The surface of the human eye has not only excellent and efficient defense mechanisms protecting against the invasion of pathogens but also against bacteria existing on the surface of the conjunctiva and skin. The main barriers protect to microbial infection are anatomical barriers (eyelids, intact conjunctiva, corneal epithelium, and tear film) and antimicrobial barriers (tear film constituents IgA, complement components, lactoferrin, lysozymes, and conjunctiva-associated lymphoid tissue (CALT)) [7]. These barriers could be disrupted and predispose to infection. Every break in the continuity of the epithelium may predispose to pathogen invasion into the cornea. Every minor injury, foreign body, or wound can be a trigger factor of inflammation.

The bacterial spectrum from different areas or periods is widely reported in the literature, and those differences could be associated with weather, rural vs. urban area, and etiology of keratitis. The most common pathogens that are associated with bacterial keratitis include *Staphylococcus aureus*, Coagulase-negative staphylococci, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and species of the *Enterobacteriaceae* family [8]. This group of bacteria is characterized a good adherence to the epithelium and to the surface of contact lenses. *Staphylococcus epidermidis* and *Staphylococcus fusarium* species are the most commonly implicated in polymicrobial keratitis with trauma being the most common inciting factor [9]. The bacterial species that can penetrate the intact corneal epithelium are *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Hemophilus aegyptius*, and *Listeria monocytogenes* [10].

Contact lens use is one of the major causes of bacterial keratitis in developed countries, whereas trauma is the main risk factor in developing countries [11, 12]. The etiology of CL-related keratitis is most commonly associated with *Pseudomonas aeruginosa* and *Acanthamoeba* species. These two types of bacteria are free-living microorganisms that are omnipresent in the environment, including water and CL solutions [13]. The risk factors of CL-related IK include: tear recession under

CL, reduction of tear exchange during blinking, and reduced corneal epithelial cell desquamation. These result in accumulation and adherence of microbes to the cornea and provide to increase risk of IK. Other local predisposing risk factors for BK are ocular surface disease (OSD), including dry eyes, corneal suture-related infection, abnormalities of eyelid anatomy and function, trichiasis, blepharitis, chronic dacryocystitis, ectropion, entropion conjunctivitis, lagophthalmos neurotrophic keratopathy, recurrent corneal erosions, epithelial defect, secondary bacterial keratitis after viral keratitis, bullous keratopathy, corneal disease, previous keratitis, xerophthalmia, blepharoconjunctivitis, fifth and seventh cranial nerve palsy. Other risk factors include mechanical or thermal injury, ocular trauma, foreign body injury, previous ocular or eyelid surgery, immunosuppression, previous corticosteroids and NSAIDs [14, 15]. Risk factors predisposing to BK are the systemic conditions such as diabetes mellitus, atopic dermatitis, connective tissue or autoimmune pathologies, Steven-Johnson syndrome (SJS), ocular mucous membrane pemphigoid (OMMP), compromised immune systems, graft-versus-host disease, immunosuppression (AIDS), chronic alcoholism, and malnourishment [16].

3. Epidemiology

The most common causative factor of IK in most regions is bacteria. BK represents the following percentage of IK, including the UK (91–93%) [17, 18], Middle East (91.8%) [19], North America (86–92%) [20], South America (79–88%) [21], and Australasia (93–100%) [22]. In the USA, the incidence of MK is 71tousends cases per year USA [23]. There is a huge disproportion in the incidence of BK between developing and developed countries. This disparity of prevalence and incidence of BK is because of differences in geographical location and environmental and climate risk factors. The contact lens' users are also significant. The pathogenesis of CL-related corneal inflammation is complex and multifactorial. CL-related IK occurs particularly in the developed and industrialized countries have been a higher frequency of contact lens' users, and as a result, there is a higher rate of contact lens-related bacterial keratitis [24, 25]. It is commonly believed that CL-related IK is caused by superficial injury secondary to CL wear. However, there are several studies in which have been shown that the presence or absence of epithelial injury did not influence the risk or severity of IK [26]. As we mentioned before, *Pseudomonas keratitis* is one of the most common causes of BK, especially in the developed countries where there is increased prevalence of CL wear.

4. Pathophysiology

The process of bacterial keratitis initiates once the epithelial is breached by any *means*. When a critical number of pathogens is exceeded, defense mechanisms fail and the stroma of the cornea is invaded by bacteria. This is facilitated by breaking the continuity of the epithelium. Only a small number of bacteria are able to break the continuous epithelium, these are gonorrhea, *Corynebacterium diphtheria*, *Corynebacterium aegyptian*, *Listeria*, and *Shigella*.

The development of bacterial keratitis progresses through four stages: stage of progressive infiltration, stage of active ulceration, stage of regression, and stage of cicatrization [27].

An important feature that determines pathogenicity is the ability of the bacterium to produce enzymes that facilitate penetration into tissues and their destruction. *Pseudomonas aeruginosa*, which produces protease, trypsin, elastase, and hemolysin, is particularly dangerous. These enzymes lead to rapidly progressing liquefied necrosis of the tissue. This bacterium should always be considered and differential as a cause of acute keratitis in CL users [25, 26, 28]. Another mechanism of tissue damage by the bacteria is the production of toxins in the form of exotoxins and the release of endotoxins after cell death that damage host cells [28]. The final course of bacterial keratitis is dependent on the virulence of the offending bacteria, host defensive mechanisms, and the treatment received.

5. Clinical features

The development of a bacterial corneal inflammation may occur as a number of clinical features. We should keep in mind that in BK signs are more common than symptoms. The common symptoms of bacterial ulcers include worsening of vision, pain, foreign body sensation, redness, watering, mucopurulent or purulent discharge, and photophobia. The various signs include lid edema, blepharospasm, mucopurulent or purulent discharge, conjunctival hyperemia and chemosis, circumcorneal congestion, epithelial defect, stromal edema and infiltrate, full-thickness infiltrate, Descemet membrane folds, hypopyon, exudates in the anterior chamber, anterior uveitis, posterior synechiae, muddy iris, and small ischemic pupil [28].

In most cases of BK, there is an epithelial defect with hyperemia and exudate mucopurulent discharge accompanied by sudden severe eye pain and photophobia. Corneal infiltrate, which causes loss of tissue transparency, as a result leads to decreased visual acuity. Inflammatory exudate may also occur in the anterior chamber of the eye and penetrate deep into the eye tissues, including the posterior segment of the eye. Such an acute course of infection with the involvement of the posterior segment of the eye occurs mainly in people with impaired immune response, using long-term steroid therapy, after eye surgery or trauma, especially after trauma with organic material. The course of the disease, as well as ocular signs and symptoms depends on the virulence of the pathogen. The increased severity of the corneal ulcer the poorer treatment results. Depending on the severity of signs and symptoms, as well as the rate of progression, BK inflammation can be divided into mild, moderate, and severe. Mild corneal ulcers <2 mm in size with the depth of the ulcer <20% or 100 μm corneal thickness that may be accompanied by superficial infiltrates near the ulcer. Moderate corneal ulcers range between 2 and 5 mm in size, depth of 20–50% (100–275 μm) of the cornea, accompanied by dense infiltrates, including the mid stroma. Severe ulcers ≥5 mm, with a depth of more than 50% (>275 μm), accompanied by dense infiltrates, include the deep layers of the corneal stroma [11, 22, 29].

The clinical features of corneal infiltration also depend on the type of pathogen that caused BK. Bacterial corneal ulceration can occure very often in the form of a single corneal infiltrate with a sharp epithelial demarcation, with a dense, purulent infiltration of the corneal stroma with indistinct borders accompanied by corneal edema. The main factors, which favor the development of bacterial ulcers with hypopyon, include the host tissue's resistance, as well as the bacteria's virulence. They occur generally in old, debilitated, malnourished, and with immunodeficiency patients.

BK caused by gram-positive bacteria, especially cocci, is characterized by a benign course with limited tissue infiltration located superficially with slight corneal swelling. They occur in patients with dry eye syndrome, blepharitis, and rosacea. They are

characterized by slow progression, but if left untreated, they can even lead to corneal perforation. Sufficient prophylaxis is the treatment of ocular surface disorders [28]. Gram-negative bacteria produce enzymes that quickly damage tissue. They are characterized by rapid progression and the lack or delayed implementation of treatment leads to complete destruction of the cornea, sclera, iris, and even loss of the eyeball. *Pseudomonas aeruginosa* usually progresses rapidly with stromal melt and necrosis, ring infiltrate, hypopyon, anterior chamber cells and flare, endothelial plaque, and later descemetocele formation or perforation [28, 30]. *Pseudomonas aeruginosa* is more common in CL-wear patients as this bacterium becomes more pathogenic in biofilm associated with the contact lens [13, 25, 26, 30]. Some bacteria cause characteristic changes in the corneal stroma, which is helpful in making the diagnosis. Streptococci cause limited infiltrates, the descent of which is crystalline keratopathy. Gram-negative bacteria, such as *Klebsiella*, *Proteus*, *Listeria*, *Streptococcus*, and *Pseudomonas*, favor the appearance of the characteristic annular shape infiltrates of the cornea [28].

6. Diagnostic tests

In the case of a diagnostic process of BK, an interview with the patient and microbiological tests are important. The clinical appearance of the infection is not a reliable factor indicating the causative pathogen. Routine proceeding should be the collection of material for culture and preparation of direct material. In patients wearing contact lenses, the contact lens itself may provide key information about the pathogen. The corneal ulcer should be cultured for the identification of the causal organism and make an antibiogram for achieve an antibiotic susceptibility before commencing antimicrobial therapy [31]. Based on the American Academy of Ophthalmology, it is still recommended to perform the first culture and/or smears in the following situations [9]:

- Infiltrates located in the central part of the cornea or large corneal infiltrate and/or associated with significant stromal involvement or melting
- Infiltrates involved a large area of the cornea (> 2 mm)
- Significant multiple infiltrates in different area of the cornea
- Previous history of corneal surgeries
- Chronic or unresponsive keratitis to broad-spectrum antibiotics therapy
- Atypical clinical features suggesting fungal, amoebic, or mycobacterial keratitis

6.1 Microbiology evaluation

The microbiological evaluation consists of smear examination and culture of corneal scrapings into several media to grow organisms for identification [32]. Culture is the only way to determine, which antibiotics the pathogenetic agent is susceptible to. In the case of sight-threatening keratitis, the culture is an indispensable diagnostic tool. The results of culture allow to shorten the duration of treatment and avoid unnecessary drug use. The efficiency of corneal cultures and smears is much higher if done before antibiotic treatment is initiated. However,

when a patient previously used antibiotics, antibiotic therapy should be discontinued and scraping can be delayed for 12–24 hours to improve test performance. Lately, calcium alginate swabs with trypticase soy broth have been employed to obtain corneal specimens for obtaining a higher yield of bacteria [33]. When obtaining specimens, we should be very careful in the case of descemetocele, deep stromal keratitis, or corneal melting. The corneal ulcer samples are performed under topical anesthesia (i.e., 1% lignocaine, 0.5% proparacaine, or proxymetacaine 0.5%). There should be preferred preservative-free formulation because preservative may lower the bacterial viability for culture. Before performing scraping, dead and necrotic tissue and loose mucus are removed from the ulcer surface. Then, the corneal ulcer samples are collected from the area of corneal infiltration (the margin and the base of the ulcer) using a disposable number 11 or 15 Bard-Parker blade or typically 25-gauge or 26 G bent hypodermic needle or sterile kimura or platinum spatula. The first samples are placed on glass slides for staining, and then onto the media for culture [12, 33, 34]. The obtained material is smeared onto one or two glass slides for microscopic evaluation along with a gram stain. Gram staining detects the type of organism in 60–75% of bacterial cases, and it is beneficial providing results in 5 minutes [12, 31]. Repeat scraping is performed, and the sample is placed on various culture media that should be taken from the fridge and left for 1 h to reach room temperature. Various stains used for bacteria and various culture media for bacteria are shown in **Tables 1** and **2** [35].

According to literature data from around the world, the positive culture rate from corneal scrapes ranges from 38 to 66% [36–42]. When smear and culture results are negative two times, and there is a clinical progression of ulcer despite the best antibacterial therapy a corneal biopsy can be performed. It is obtained with the help of a dermal trephine or freehand dissection, and the specimen is divided into two halves to

Gram stain	Gram-positive bacteria appear purple and gram-negative as pink
Acridine orange	Bacteria appear as yellow-green
Acid Fast	Mycobacterium appear as pink

Table 1.
Various stains used for bacteria.

Blood agar (35 degrees)	*Aerobic* and facultative *anaerobic* bacteria
Chocolate agar (35 degrees)	*Aerobic*, *anaerobic*, *Neisseria*, *Moraxella* and *Haemophilus*
Thioglycolate broth (35 degrees)	*Aerobic* bacteria and *Anaerobic* bacteria
Sabouraud's dextrose agar (Room temperature)	*Nocardia*
Brain heart infusion broth (Room temperature)	*Nocardia*
Middlebrook Cohn agar (35 degree with 3 to 10% CO_2)	*Mycobacterium* and *Nocardia*
Cooked meat broth (35 degrees)	*Anaerobic* bacteria
Thayer martin blood agar (35 degrees)	*Neisseria*
Lowenstein Jensen media (35 degrees with 3 to 10% CO_2)	*Mycobacterium* species

Table 2.
Various culture media for bacteria.

allow histopathological and microbiological analysis [9, 43]. Conjunctival swab culture (calcium alginate swabs give the best results) may be another important additional diagnostic method in severe cases when culture growth is negative [44]. Anterior chamber paracentesis is another needed diagnostic method, which is performed in the case of negative scraping culture, or there is a progression of ulcer despite the best antibacterial therapy. A 0.1 to 0.2 ml sample is obtained with the help of a 25 G needle by a side port [45]. In addition to corneal scrapping, it is worth to obtain culture from contact lenses, liquids, and containers for lenses and from other potential sources of infection, for example, from inflamed eyelids. A relationship has been demonstrated between cultures of the abovementioned sources and corneal scraping [46]. We should keep in mind, that as interpreting results caution is needed because most eyelid and ocular surface commensal organisms are gram-positive and likely to contaminate the sample [47].

6.2 Polymerase chain reaction test

The polymerase chain reaction (PCR) test is another test used in the diagnosis of microbial keratitis. This is a molecular technique for the detection and analysis of specific DNA sequences, consisting of repeated cycles of denaturation, amplification, and replication, in which segments of DNA are continuously multiplied to enable their detection [48]. The advantages of PCR, including sensitivity, speed, and cost-effectiveness relative to culture and staining. It also gives an ability to quickly differentiate bacterial and fungal ulcers. It also gives a possibility to detect of slow-growing bacteria and organisms that are difficult to cultivate or identify with traditional microbiological methods [49–51]. This technology also has an important role in diagnosing rare organisms, such as atypical mycobacteria and Nocardia species [52]. There are also some disadvantages, including the high rate of false positive errors from commensal contaminants or dead bacteria, lower specificity compared with culture and staining, difficulty to interpret results and treating by clinician, more expensive procedure, and less cost-effective when performed with a multi-organisms PCR approach, and is not readily available at all sites [49–51].

6.3 *In vivo* confocal microscopy (IVCM)

In vivo confocal microscopy (IVMC) is a noninvasive examination that shows real-time visualization of corneal layers and structures and pathological agents within the corneal tissue. The advantages of IVCM are repeatability, rapidity, and noninvasiveness, thus also being useful in monitoring the therapy. The high sensitivity and specificity of IVCM is a valuable adjuvant to the other diagnostic assays. Thanks to immediate results obtained after conducted rapid in vivo corneal examination, it allows the prompt beginning of appropriate treatment, and some authors recommend its use as a very good diagnostic tool early in the course of the disease [53]. IVCM is also useful appreciate the depth of the infection in the corneal stroma, what is an important prognostic factor of IK [54]. However, there are some disadvantages that include patient collaboration and patience are required during testing, the high price of the device, lack of availability at all sites, and difficulty in both acquiring and interpreting images by non-experienced clinician [54]. When we have access to IVCM, we should always consider to perform this examination in the following clinical situations: deeply situated infiltrates, where corneal scrapes do not have access to avoid invasive corneal biopsy, MK occurring after corneal surgery (i.e., intracorneal implants, refractive surgery), lack of the positive results in current

treatment with antifungal or anti-*Acanthamoeba* spp. therapy, when actively proliferating microorganisms are found in the profound, inaccessible corneal stroma [53, 54]. IVCM is highly sensitive and specific, and thus is very useful in cases of fungal or *Acanthamoeba keratitis*. As for nowadays, IVCM should be used alongside cultures and smears. Other new diagnostic modalities, such as immunohistochemistry, enzyme immunoassay, and radioimmunoassay, are recent upcoming modalities but still have a limited role in diagnosing BK [55].

7. Treatment

The most important goal of medical treatment is to preserve vision and maintain corneal transparency. The medical treatment of a BK should be started promptly before the etiological agent is known. The initial treatment is usually empiric as culture results can take over 48 hours, and the infection can progress rapidly without treatment. All patients should start on broad-spectrum antibiotic therapy, covering both gram-positive and negative bacteria after obtaining the smear results. Due to the high probability of bacterial etiology, in doubtful cases of fungal and viral infections, an antibiotic is also used in addition to drugs against these pathogens. In the case of severe infections characterized by heterogeneous bacterial flora or in the case of larger and deep stromal ulcers, it usually prompts the use of two broad-spectrum antibiotics to prevent irreversible vision-threatening sequelae. The antibiogram, which we obtain a few days after the implementation of empirical treatment, allows to verify the initial diagnosis and decide whether to continue or modify the initial treatment. Treatment should be changed based on the results of culture and susceptibility testing. Different indications in the antibiogram should not lead to a change in the treatment profile if there is observed a clinical improvement after the implementation of empirical treatment [12].

7.1 Antibiotics

The main goal of treatment is broad-spectrum topical antibiotics, which should be used until culture results are available. The basis of the therapy is obtaining high concentrations of antibiotics within the infected tissue. For severe BK, an initial frequent dosage every 5–15 min is recommended. Thus, the eye drops are applied even hourly in the first day of therapy. At the beginning of therapy, in order to increase the effectiveness of the therapy, eye drops with a higher concentration of the drug (fortified eye drops) are often used than in commercial usage.

The main group of antibiotics used in bacterial keratitis is fluoroquinolones. Fluoroquinolones are the group of antibiotics that provide excellent tissue penetration, quickly reaching high concentrations within tissues and have a broad spectrum of bactericidal activity. There are four generations of fluoroquinolones, of which the broadest spectrum of activity has the fourth generation of fluoroquinolones, including moxifloxacin and gatifloxacin. Within the third generation, the commercially available drug is levofloxacin. Treatment can also be carried out using second-generation drugs, that is, which is the drug of choice in gonorrhea infections. The AAO BK Preferred Practice Pattern, the Royal College of Ophthalmologists Focus, UK initially recommends monotherapy with fluoroquinolones (ciprofloxacin 3 mg/ml, ofloxacin 3 mg/ml, moxifloxacin 5 mg/ml, levofloxacin 15 mg/ml, gatifloxacin 3 mg/ml, or besifloxacin 6 mg/ml). An alternative includes a combination of cephalosporin or vancomycin plus and an aminoglycoside. Vancomycin should be used in the case of

multidrug resistant gram-positive isolates [9, 31]. Lately is noted increasing resistance for ofloxacin and ciprofloxacin; hereof, moxifloxacin and gatifloxacin are being used with more efficacy in managing bacterial keratitis [56].

Aminoglycosides are the second group of antibiotics that should be considered when treating BK. Aminoglycosides are represented by amikacin 0,3% topical eye drops (fortified amikacin eyedrops: 40 mg/ml), neomycin 0,5% eye ointment, gentamicin 0,3% topical eye drops (fortified gentamicin eye drops: 14 mg/ml (1.4%)), and tobramycin - 0,3% topical eye drops (fortified tobramycin eye drops: 14 mg/ml (1.4%)). Due to the broad spectrum of activity against gram-positive bacteria (excluding streptococci and pneumococci) and gram-negative bacteria, they are combined in the first line with fluoroquinolones. The mechanism of action of the fluoroquinolones is blocking of topoisomerase IV and DNA gyrase. The mechanism of action of aminoglycosides is to block protein synthesis at the ribosomal level. The combination of antibiotics from both groups is effective in the treatment of an unspecified etiological factor.

Other antibiotics that demonstrate a high therapeutic effectiveness in BK is vancomycin, which is used in severe infections. Fortified vancomycin 5% is very active against methicillin-resistant *Staphylococcus aureus* (MRSA). Whereas topical cefazolin 5% (fortified) is best appropriate for non-penicillinase-producing gram-positive bacteria [56].

The systemic antibiotics have indications in non-resolving progressive bacterial ulcers, especially with associated scleritis or endophthalmitis [57]. Fluoroquinolones, which demonstrate excellent penetration into ocular tissues when combined with intensive topical antibiotic treatment, are especially recommended.

7.2 Topical corticosteroid therapy

The use of additional adjuvant topical corticosteroid therapy remains still controversial [12, 58]. When the disease process is advanced and tissue necrosis occurs, or when inflammation is accompanied by intense cellular inflammatory infiltration into the cornea, weak steroids could be used. Topical corticosteroid therapy should be used with caution under constant clinical observation of the patient's involving eye because it may worsen the infection, local immunosuppression, corneal melting, and increased intraocular pressure [9, 58]. Topical corticosteroid therapy is used as an aim of suppression of inflammation to reduce corneal scarring, neovascularization, and vision loss. Hence, common or indiscriminate use of corticosteroids is inappropriate; however, it do not appear to increase the overall risk of failure or management of BK.

7.3 Other topical drugs therapy

Cycloplegics medications are commonly used as adjuvant drugs to relieve the pain, reduce ciliary spasm, and reduce cells and flare, as well as to prevent posterior synechiae formation that is often associated with iritis accompanying BK. They are indicated in cases with significant anterior chamber inflammation [12, 55, 56]. Antiglaucoma drugs are useful to control and reducing intraocular pressure by help drain the hypopyon by opening the trabecular meshwork and drainage channels, as well as to help in controlling trabeculitis secondary to the inflammatory process. A total of 0.5% timolol is commonly used. Two groups of topical drugs should be avoided, namely prostaglandin analogs and miotics because they exacerbate inflammation of the eye [12, 55, 56].

There should also be taken care of basic hygiene measures, which include careful removal of residual purulent secretion, which contains enzymes from decayed and

endotoxins of dead bacteria, which makes it difficult for drugs to penetrate into the tissues. The moisturizing of the eye surface with the use of artificial tear preparations, that purpose is to restore disturbed homeostasis of the eye surface, as well as to help epithelial healing, reduce irritation, wash away debris and necrotic enzymes, and smoothen the ocular surface and cornea are also important.

7.4 Surgical treatment

Corneal cross-linking (CXL) is a relatively new option for anti-infective treatment, especially in cases of superficial bacterial keratitis, and is increasingly used as an additional adjuvant treatment, which has been confirmed in clinical trials [59–61]. The interaction of UV light and riboflavin damages the DNA and RNA of bacterial and viral pathogens and prevents their protein synthesis and replication, leading to the death of the microorganism [62]. Moreover, the cornea after CXL is more resistant to proteolytic enzymes produced by bacteria [63]. CXL, besides as adjuvant treatment for BK, can be also used as primary treatment in the early stages of infectious ulcerative keratitis. PACK-CXL (photoactivated chromophore for keratitis) is the procedure that uses of CXL besides the Dresden protocol for the treatment of infectious keratitis [60]. PACK-CXL, as an additional to the standard of care in cases of culture-proven bacterial keratitis, has a positive effect on the final visual acuity and time to resolution, compared with the standard-of-care treatment [64]. Recently studies reported that CXL therapy for IK patients with corneal thinning and/or including anterior part of the stroma is promising procedure [65].

There are several cases in which surgical interventions are indicated. The application of cyanoacrylate tissue adhesive is the first-line intervention for corneal perforation, providing a successful tectonic support for a short time, although requiring reapplication with a month after first application [66]. Depending on the cause of the perforation, indications for applications, and definition of success the success of this adhesive ranges between 29% and 86% [66].

Amniotic membrane has a great effect in acceleration corneal healing. Amniotic membrane transplantation (AMT) is an alternative therapeutic treatment option to cyanoacrylate glue application along with bandage contact lens (BCL) in the case of impending corneal perforation or corneal perforation [66, 67]. Although in the case of larger perforation (>2 mm), therapeutic keratoplasty should be performed.

Conjunctival flap (Gunderson flap) is another alternative treatment in the case of impending corneal perforation or corneal perforation if a donor cornea is unavailable. Conjunctival flap is considered as one of the oldest methods to treat corneal perforation when access to corneal graft is impossible [68]. In order to implement the accurate role of the conjunctival flap in treatment before keratoplasty in cases of BK there are needed extra studies. The technique relies on dissection of the upper conjunctiva, and a thin flap of the conjunctiva is covered over the cornea and sutured [69].

Therapeutic penetrating keratoplasty is used in the treatment of BK and is indicated when the disease progresses despite treatment, nonhealing corneal ulcers (above 2 weeks), descemetocele or perforation occurs, or keratitis does not respond to antimicrobial treatment [70]. Therapeutic penetrating keratoplasty helps eliminate the focus of infection and as a tectonic keratoplasty restores anatomical integrity in perforated corneal ulcers. During the procedure, it is advisable to remove all areas of infection and perform peripheral iridectomy because the pupil may be secclusio due to inflammatory membranes in its lumen. When exudates are present in the lens or there is a cataract, then the lens is removed. If the posterior capsule is tact, a thorough anterior vitrectomy

is made. Clearing corneal margin of 0.5 mm from the diseased cornea is removed and put the graft is kept 0.5 mm larger than the host cornea. It is recommended to use single seams (9–0 or 10–0 nylon). After the procedure, topical antibiotics, cycloplegics, and topical steroids are used. Although the probability of graft survival is reduced in about a half, at 4 years post-intervention, in eyes with inflammation or with corticosteroid use at the time of graft, therapeutic penetrating keratoplasty remains the major intervention for the management of rapidly progressing severe infections and in large corneal perforations [67, 70]. When the visual acuity is poor, the cornea has scarred and healed and the infective foci have been eliminated after BK treatment penetrating keratoplasty (PKP) can be performed in order to restore the patient's vision. PKP is possible to conduct after 6 to 8 months of quieted after BK treatment [70].

7.5 Alternatives methods of treatment

In the literature based on animal studies showed that cryotherapy may have a possible advantageous result on BK involving the sclera. Although more studies about cryotherapy on the human cornea are still essential to answer for its efficacy and safety on human corneas [71, 72].

Mitomycin C (MMC) is an antimetabolite isolated from Streptomyces caespitosus. MMS has been successfully used in refractive surgery to reduce postoperative corneal haze and scaring due to its anti-fibroblast activity [73]. In one research, authors found that MMS has a broad-spectrum antimicrobial activity against a broad range of bacteria, including *E. coli*, *S. aureus*, and *P. aeruginosa* [74]. However, further studies are required to evaluate the effect of MMC on human corneas in BK because above mentioned results from laboratory studies are limited. While the inflammation process (i.e., an acute infection) and inflammatory cells (such as keratocytes, fibroblasts) produce enzymes: collagenases and matrix metalloproteinases (MMPs) that are involved in protein degradation and keratolysis. Anti-collagenases are promising adjuvant option in treatment BK though there are no high-quality randomized controlled trials in humans to help clinicians in the use of doxycycline for the corneal ulceration treatment, although its widespread use among corneal specialists [75–77].

Antimicrobial photodynamic therapy is another new approach for IK treatment based on three agents: oxygen, light radiation, and photosensitizer. Photodynamic therapy has proved as an effective therapy against infectious agents it does not present selective pressure on resistance development by both gram-positive and gram-negative bacteria. Thus, this new treatment option has an unusual potential for treatment of BK cases that have not achieved a good response after traditional antibiotic therapy [78].

In the newest reports, the bacteriophage therapy is growing as an effective alternative to treat ocular infections. A variety of nanotechnology-based formulations, such as nanoemulsions, liposomes, polymeric nanoparticles, dendrimers, and nanofibres, have been recently reported to be effective results in bacteria resistance to antibiotics. There are bacteriophage-based nanoformulation techniques for the successful treatment of ocular infections caused by multidrug-resistant S. aureus and other bacteria [79].

8. Conclusions

Corneal opacity represents the fifth leading cause of blindness globally, with infectious keratitis being the main culprit. Bacterial keratitis is a severe condition of the eyes that could have a burden impact on human health in both developed and

developing countries. Understanding of the major risk factors for BK particularly CL wear, trauma, ocular surface diseases, and postocular surgery will simplify a more effective public health intervention to modify and reduce the risk of BK. Early and prompt medical treatment is needed to avoid complications. The vision-threatening bacterial ulcers, if treated on time, can have an excellent visual effect. In the past few decades, it has been observed the increased rate of antimicrobial resistance (AMR) in ocular infection in several countries highlights the need for reasonable use of antibiotics. It should be a tighter control of OTC antibiotics and development of new therapeutic strategies. Improvement in the diagnostic efficiency of microbiological investigations of BK with emerging new technologies will allow for fast and proper diagnosis and could also provide a better guidance on the appropriate use of antimicrobial therapy in the future, eventually reducing the risk of AMR. The prognosis of BK is governed by a multiplicity of factors. The good prognosis for BK is in the case of bacterial ulcer located in the superficial corneal layers (anterior one-third of the stroma), as well as a result of a good compliance between doctor and patient and regular follow-up, and regular use of medications. Involvement of sclera or endophthalmitis, ulcer involving more than two-thirds of stroma, located in the visual axis, stromal melt, and corneal thinning exacerbate much more the prognosis. New approaches for the treatment of bacterial keratitis are necessary to outcome the increasing antibiotic resistance.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

BK	bacterial keratitis
IK	infectious keratitis
MK	microbial keratitis
OSD	ocular surface disease
CL	contact lens
AMR	antimicrobial resistance
PCR test	polymerase chain reaction test
IVCM	*in vivo* confocal microscopy
CXL	corneal cross-linking
PACK-CXL	photoactivated chromophore for keratitis
PKP	penetrating keratoplasty
AMT	amniotic membrane transplantation
MMC	mitomycin C
MMPs	matrix metalloproteinases

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