Clinical Interventions in Aging

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REVIEW

Infectious Keratitis in Patients Over 65: A Review on Treatment and Preserving Eyesight

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Abstract: Infectious keratitis (IK) represents a significant global health concern, ranking as the fifth leading cause of blindness worldwide despite being largely preventable and treatable. Elderly populations are particularly susceptible due to age-related changes in immune response and corneal structure. However, research on IK in this demographic remains scarce. Age-related alterations such as increased permeability and reduced endothelial cell density further compound susceptibility to infection and hinder healing mechanisms. Additionally, inflammaging, characterized by chronic inflammation that develops with advanced age, disrupts the ocular immune balance, potentially exacerbating IK and other age-related eye diseases. Understanding these mechanisms is paramount for enhancing IK management, especially in elderly patients. This review comprehensively assesses risk factors, clinical characteristics, and management strategies for bacterial, viral, fungal, and acanthamoeba keratitis in the elderly population, offering crucial insights for effective intervention.

Keywords: aging, inflammaging, bacterial keratitis, viral keratitis, fungal keratitis, acanthamoeba keratitis

Introduction

Infectious keratitis (IK) is an infection of the cornea classified by its various microbial and viral etiologies.[1] It is the fifth leading cause of blindness worldwide, even though it is a preventable and treatable condition.[1] According to the most recent World Health Organization (WHO) report, approximately 6 million people suffer from corneal diseases like infectious keratitis, resulting in visual impairment globally.[2] In the United States alone, nearly 71,000 new cases of IK are diagnosed annually.[3] IK affects all age groups, and prevalence of IK is generally low at the extremes of age, such as in children and the elderly. However, studies have demonstrated worse visual outcomes and higher complications in the elderly. This vision-threatening condition imposes a significant global burden, affecting both developed and developing nations.[4] Although accurately quantifying the burden is challenging, a 2010 report revealed that IK contributes to approximately 1 million healthcare provider visits and 58,000 emergency department visits in the United States, with an estimated cost of $175 million.[4,5] Among these, $58 million were expenditures for Medicare patients.[2]

The incidence of various causative agents of IK vary depending on geographic region, socioeconomic conditions, and individual lifestyle factors like contact lens usage.[3] Age and comorbid health conditions, which tend to increase in older populations, are risk factors that may affect the clinical course and treatment of IK. A retrospective study spanning 32 years on microbial keratitis in the elderly found that past ocular surgery was the primary contributing factor.[3] Another retrospective review revealed that low activities of daily living and social environment were significant contributors to developing IK.[4]

Elderly patients experience changes in immune response, alteration of the lids and conjunctival flora, poor lacrimal drainage, fragility of the corneal epithelium, and reduction of corneal sensitivity, among others.[3] These age-related changes may put elderly patients at higher susceptibility to certain causative agents of keratitis, as well as worse outcomes. Despite the severity of IK in this population, studies on keratitis in older patients remains scarce.[5] Thus,

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this review aims to summarize the current literature on age-related changes in the cornea and differences in risks and management of elderly patients with infectious keratitis.

Aging and the Cornea

Corneal age-related changes may alter its ability to refract light, undergo self-repair, and protect both itself and intraocular structures.[6] These alterations render the aging cornea more vulnerable to infections. With age, there's an increase in epithelial permeability, potentially indicating either a breakdown in the epithelial barrier function[7] or prolonged tear contact time.[8] Changes in the distribution of integrin subunits within the epithelium, particularly the discontinuity of the α6 and β4 subunits of hemidesmosomes, have been studied.[9] However, the overall number and distribution of hemidesmosomes along the basal lamina do not seem to change. Diminished upregulation of adhesion molecules by corneal cells and reduced phagocytic activity of reactive polymorphonucleocytes further compromise the ability to combat bacterial infections.[10]

The effects of aging on the cornea are also significant regarding corneal innervation and sensation. A reduction in corneal sensitivity, due to factors such as aging, can result in ocular surface abnormalities that increase susceptibility to corneal infections and impair wound healing. According to Yang et al, aging is associated with a reduction in corneal nerve density and sensitivity, compromising ocular surface homeostasis.[11] Additionally, Chin et al found a decline in corneal nerve fiber length and density in patients aged 65 or older, further emphasizing the importance of considering age-related factors in ocular health.[12] These studies highlight the need for more research on how aging affects the corneal nerve and overall ocular surface health.

Studies have also shown a reduction in endothelial cell density with advancing age. While the precise biological mechanisms are unknown, hormonal fluctuations, environmental factors, and degradation of enzymes in the anterior segment, responsible for metabolizing and detoxifying free radicals, result in delayed recovery from hypoxic stress by the aging cornea. Moreover, the corneal endothelium, vital for maintaining corneal transparency by regulating water content, faces reduction in endothelial cell density with normal aging, accentuated by infection, inflammation, or surgery, such as phacoemulsification, common for patients in this age group.[13,14] The key findings of aging and the cornea are summarized in Table 1.

Table 1 Age-Related Changes in the Cornea and Ocular Adnexa

Study Type	Key Findings	Citation
Literature review	Age-related corneal changes increase vulnerability to infections.	Faragher RGA, Mulholland B, Tuft SJ, Sandeman S, Khaw PT. Aging and the cornea. *Br J Ophthalmol*. 1997;81(10):814–817. doi:10.1136/bjo.81.10.814.[6]
Cross-sectional observational study	Aging increases epithelial permeability, indicating barrier breakdown or prolonged tear contact.	Chang SW, Hu FR. Changes in Corneal Autofluorescence and Corneal Epithelial Barrier Function With Aging. *Cornea*. 1993;12(6):493.[7]
Observational study;[9] Controlled laboratory experimental study[10]	Changes in integrin subunits and reduced adhesion molecule upregulation, phagocytic activity.	Trinkaus-Randall V, Tong M, Thomas P, Cornell-Bell A. Confocal imaging of the alpha 6 and beta 4 integrin subunits in the human cornea with aging. *Invest Ophthalmol Vis Sci*. 1993;34(11): 3103–3109.;[9] Hobden JA, Masinick SA, Barrett RP, Hazlett LD. Aged mice fail to upregulate ICAM-1 after Pseudomonas aeruginosa corneal infection. *Invest Ophthalmol Vis Sci*. 1995;36(6):1107–1114.[10]
Literature review	Aging reduces corneal sensitivity and nerve density, impairing wound healing.	Yang AY, Chow J, Liu J. Corneal Innervation and Sensation: The Eye and Beyond. *Yale J Biol Med*. 2018;91(1):13–21.[11]
Cross-sectional observational study	Decline in corneal nerve fiber length and density in patients aged 65 or older.	Chin JY, Liu C, Lee IXY, et al. Impact of Age on the Characteristics of Corneal Nerves and Corneal Epithelial Cells in Healthy Adults. *Cornea*. 2024;43(4):409. doi:10.1097/ICO.0000000000003363.[12]

(*Continued*)

Table 1 (Continued).

Study Type	Key Findings	Citation
Prospective, randomized, comparative study	Reduced endothelial cell density with age.	Hepokur M, Bulut Kizilay E, Durmus E, Aykut V, Esen F, Oguz H. The influence of corneal incision size on endothelial cell loss and surgically induced astigmatism following phacoemulsification cataract surgery. *North Clin İstanbul*. 2022;9(4):385–390. doi:10.14744/nci.2021.81084.[13]
Retrospective cohort study	Endothelial cell density reduction due to aging, infection, inflammation, or surgery.	Kwon JW, Cho KJ, Kim HK, et al. Analyses of Factors Affecting Endothelial Cell Density in an Eye Bank Corneal Donor Database. *Cornea*. 2016;35(9):1206. doi:10.1097/ICO.0000000000000921.[14]
Review	Age-related eyelid malposition (entropion and ectropion) increases risk of ocular irritation.	Hakim F, Phelps PO. Entropion and ectropion. *Dis Mon*. 2020;66(10):101039. doi:10.1016/j.disamonth.2020.101039.[16]

Aging and the Ocular Adnexa

The ocular adnexa include the eyelids, conjunctival sac, lacrimal drainage system, lacrimal gland, and all orbital contents excluding the eye and optic nerve.[15] These structures undergo age-related changes that can predispose patients to developing infectious keratitis. Eyelid malposition disorders, such as entropion and ectropion, are particularly common in the aging population (Table 1).[16] Entropion is the inward rotation of the eyelid margin, leading to misdirected eyelashes and keratinization of the margin. In contrast, ectropion involves the outward rotation of the eyelid margin.[16] Both conditions stem from the age-related degeneration of periocular tissues.

Older individuals are also more likely to have undergone blepharoplasty for functional or cosmetic reasons. A potential complication of this surgery is lagophthalmos,[17] which is characterized by incomplete or abnormal eyelid closure. Lagophthalmos can occur immediately postoperatively or develop later in life as eyelid laxity increases, leading to incomplete eyelid closure. Patients with lagophthalmos are unable to close their eyes completely, which can result in corneal exposure and subsequent exposure keratopathy. This condition is a risk factor for persistent epithelial defects of the cornea, potentially leading to secondary infectious keratitis. Therefore, it is crucial to recognize these ocular adnexal changes, such as lagophthalmos and other eyelid malpositions, that occur in the elderly as they are significant risk factors for developing infectious keratitis.[18]

Inflammaging

While it is well-established that immunity declines with age, the specific effects of aging on corneal immune response, particularly concerning inflammatory cells like dendritic cells, remain uncertain.[19] Inflammation has been described as the core of the aging process, and related, interconnected pillars include metabolism, stress, epigenetics, and macromolecular damage. A focus of recent aging research has been inflammaging, a term that describes the age-related change in inflammation that is chronic and persistently stressful to the immune system.[20] While prolonged levels of inflammation are harmful to health in the long-term and contributes to diseases such as diabetes,[21,22] malignancy,[23,24] and dementia,[25,26] some acute inflammation is necessary to clear infections and appropriately heal injuries. Pro-inflammatory responses are particularly important in the cornea. Activation of the innate immune system and production of chemokines and cytokines normally protect the cornea and prevent pathogenic infiltration that leads to infection.[27] When the cornea has been invaded by pathogens in infectious keratitis, immune cells and their signaling cascades function to clear microbes and promote tissue healing. If these primary defenses fail, such as when macrophages and dendritic cells are low or pro-inflammatory receptors like toll-like receptor 4 are impaired during *Pseudomonas* keratitis, bacterial clearance is reduced.[28,29] Studies show that these immune cells can fail with age, as seen in polymorphonuclear neutrophil function in *Pseudomonas* infection.[30,31]

Immune homeostasis at the ocular surface occurs through tight regulation of inflammatory factors including inflammatory cytokines like IL-1, IL-6, and TNF-a,[32] molecules such as Fas ligand,[33] neuropeptides,[34] and dendritic and Langerhans cells.[35] This intricate balance of inflammation becomes dysregulated with aging[36,37] and becomes the basis for which specific eye diseases present at greater prevalence with increased age, such as dry eye.[38,39] Furthermore, immunosenescence correlates with reduced T cell responses and diminished production of cytokines like IL-2 and IL-3, while also coinciding with heightened levels of IFN-γ and TNF-α.[40] This imbalance in the local T cell and cytokine environment may potentially enhance susceptibility to HSV keratitis.

Also at the ocular surface are many natural processes that protect the eye from the environment. The functional unit responsible for this is comprised of numerous structures and has been referred to as the "Ocular Surface System". It includes the eyelids and eyelashes that mechanically keep debris away, the glandular systems, the epithelia, and the tear film, which lubricates the cornea to maintain light refraction capability, protects from epithelial defects, and secretes anti-inflammatory and antimicrobial molecules,[41] among many other functions. Together, these structures are responsible for preventing epithelial cell invasion by pathogens and must be intact for a healthy corneal epithelium. With age, unfortunately, these structures become functionally altered[42–44] and are less effective defenses to the outside world. The cornea becomes more vulnerable to infection and prone to injury with time, and corneal healing is also impacted. Corneal re-epithelialization is facilitated by activity within the limbus region of the basal epithelium where stem cells are located,[45] and these limbal stem cells have reduced proliferation with increasing age.[46] With time, the cornea becomes more vulnerable to injury and infection and is slower to heal, making severe corneal infections more likely.

Characteristics and Treatment of Infectious Keratitis in the Elderly

Bacterial Keratitis

Bacterial keratitis (BK) has a bimodal distribution with increased prevalence in the young and old.[45] Among patients age > 65 years, there does not appear to be a sex predilection, as revealed by a study across various US centers between 1977–1984.[47] This is consistent with the finding that BK has equal sex distribution overall when patients of all ages are analyzed.[48]

The predominant bacterial isolates in BK and trends in pathogen-type vary by geographic location and with time. For instance, across similar periods in time, Toronto has had decreasing gram-positive isolates[49] while Taiwan has had increasing gram-positive and decreasing gram-negative isolates.[50] Despite regional variations, isolates globally are more frequently gram-positive with coagulase-negative *Staphylococcus* species being most common.[51] This is especially the case for older patients. When corneal scrapings from BK patients were performed by Soleimani et al, they identified *Pseudomonas aeruginosa* most commonly, but *Streptococcus pneumoniae* was most prevalent in samples of patients > 50-year-old.[52] Similar results were found by Parmar et al. While not the leading cause of BK in older patients, *Pseudomonas* is a leading cause of gram-negative keratitis in this age group.[31,47,53] Its invasive strain occurs at a higher frequency in elderly males with BK compared to cytotoxic strains, which are more frequently seen in < 50-year-old individuals.[54,55] There is a predilection for the invasive *Pseudomonas* strain in older patients, and when combined with the more aggressive clinical disease of invasive strains compared to cytotoxic strains,[55,56] older patients typically have worse outcomes.

Rarely does bacterial keratitis occur without a predisposing factor. Ting et al found that patients presenting with BK who are > 50 years old had similar numbers of predisposing risk factors as younger patients, with the majority of them having one risk factor (66.1% in ≤ 50 years, 67.3% in > 50 years).[57] However, significant differences in the type of risk factor was seen between these age groups. In younger populations, the leading causes of bacterial keratitis include contact lens use[57] and corneal trauma,[45,58] which are less commonly seen in older adults.[59] The primary risk factors in older populations are immunosuppression, which can come from diabetes, use of systemic immunosuppressive drugs, malnutrition, and immunodeficiency,[57] and predisposing ocular surface conditions[45,57,60] like corneal scarring,[47] corneal transplant,[59] and ocular surgery.[59,61] Of note, aging itself causes a relative state of immune alteration, as mentioned previously, and predisposes to ocular surface disease. A shift toward systemic factors, immune system changes, and ocular surface disease, then, provides some explanation for the age-related risk for BK in older adults.

Patients > 65 years with bacterial keratitis also vary from their younger counterparts in initial clinical presentation and risk for complications. On initial presentation, older patients with BK have worse vision and more severe disease.[45,57] Among cases of microbial keratitis, worse outcomes are more likely in older patients with poor visual acuity and larger epithelial defects on presentation.[59] The elderly age group has also been seen to have an increased probability of 90-day visual impairment (VA < 20/40).[62] These trends in microbial keratitis are also seen in the subgroup of bacterial keratitis where elderly patients have poor visual outcomes compared to individuals < 65 years. Specifically, Ly et al reported that their poor outcome subgroup had an average age of 67 years compared to 50 years.[63] Furthermore, older patients have higher rates of poor healing when > 50 years,[57] and greater rates of complications and surgical intervention when > 65 years.[45]

Parmar et al found that patients > 65 years had similar incidence of fungal and bacterial keratitis, but presented with higher incidence of central, severe ulcers and poor visual acuity compared to younger patients.[5] This finding of similar incidence but worse outcomes in older patients is due to a multitude of reasons including more invasive strains of pathogens[55,56] and worse clinical disease like severe, central ulcers.[5] Importantly, immunity decreases with increasing age, and corneal healing is impacted by age.[37,46,57] Furthermore, as individuals age, the ability of their cornea epithelium to heal following damage, such as from keratitis, is much reduced.

The pathophysiology of bacterial keratitis has been studied by Narimatsu et al using a murine model of BK using *Pseudomonas*.[64] They found that improvement in clinical disease, as seen as reduced cornea edema, is associated with greater corneal lymphangiogenesis, which involves increased expression of pro-lymphangiogenic factors (VEGF-C, VEGFR-3) and F4/80 and CD11b-positive macrophage activity. They also discovered that bacterial activity is not directly involved in later stages of disease. This means that when disease becomes severe, which more often occurs in older patients, as previously stated, infection clearance and clinical improvement is reliant on immune system activation and systemic responses. Older patients are, consequently, vulnerable to worse clinical disease and poor outcomes from BK due to their impaired corneal immunologic activity and higher prevalence of predisposing ocular surface diseases.

The diagnosis of keratitis is reliant on smears and cultures from corneal scrapings, which provide microbial information to guide management. While they often have a low yield[65] and take multiple days to result, they remain the gold standard for diagnosis. Interestingly, Ting et al and other investigators have found an association between positive culture results in bacterial keratitis and increased age,[66] larger ulcer size and central location, topical steroid use,[67] no prior antibiotic treatment,[66] and worse visual acuity on presentation.[57] While specificity and sensitivity reports in elderly patients have not been studied, the correlation between positive culture results and increasing age, and the evidence that older individuals have more severe disease could suggest greater microbial burden on presentation. Corneal scrapings should continue to be obtained in older- patients suspicious for BK, until more rapid, specific, and sensitive testing modalities are available.

The treatment of bacterial keratitis is dependent on microbiology testing and susceptibilities, but it often begins with empiric topical antibiotics. In patients with bacterial keratitis secondary to gram-positive cocci, levofloxacin susceptibility has been found to decline with age beginning at age 40.[68] This age-related resistance, which likely develops with fluoroquinolone exposure over time, is important to keep in mind as patients who do not improve may need modifications to antibiotic dosage or class. They may also require more intensive medical treatment, as seen in the study by Ballouz et al who found older age to be associated with greater drops of medication prescribed.[69] Similarly, Parmar et al identified higher percentages of ulcers healing with medical treatment only in children than older individuals. Of note, older patients have a higher risk of topical ciprofloxacin deposition in the cornea, which can delay epithelial healing by 55% but has not been seen to affect time to improvement.[70] It becomes necessary, then, to closely follow BK in older patients, who may need adjustments to management and more intense regimens.

Whether empiric steroid therapy is appropriate while culture results are still pending, and whether they provide more benefit than harm, is an important area of investigation among older patients who are already at greater risk for poor outcomes from BK. The Steroids for Corneal Ulcers Trial (SCUT) found that adjunctive topical corticosteroids for bacterial corneal ulcers were safe and associated with improved clinical outcomes at 3 and 12-months.[71–73] However, the SCUT trial analyses lacked stratification by age. Given the paucity of studies specific to older patients with BK, ophthalmologists must consider whether the use of topical steroid regimen efficacy in the SCUT trial is generalizable to the older patient.

Viral Keratitis

Viral keratitis is one of the most prevalent forms of infectious keratitis, with herpes simplex virus (HSV) being the predominant etiologic agent.[74] Other common causative pathogens include the beta-herpesvirus cytomegalovirus (CMV), the alpha-herpesvirus varicella-zoster-virus (VZV), and the gamma-herpesvirus Epstein-Barr virus (EBV).[74] The alpha-subfamily, which includes HSV and VZV, known for their broad host range, remains latent in sensory neurons until reactivation.[75] This section will specifically address the clinical progression and treatment of Herpes Simplex Keratitis (HSK) in the elderly, as both the clinical characteristics and therapeutic approaches have been extensively studied for HSK within this demographic.

Although primary HSV-1 infection traditionally occurs during childhood, several studies demonstrate a rising trend in older individuals,[76] considering predisposing factors such as immunosuppression, advancing age, sun overexposure, family history, trauma and ocular surgery.[1] A retrospective study in patients 60 years and over demonstrated significant HSV-associated morbidity in the elderly, either as a predisposing factor to other types of keratitis, in polymicrobial infection, or as the single causative pathogen. This increased susceptibility may be attributed to natural age-related changes and comorbid conditions that cause immunosuppression. As immunity declines with age, the impact of herpetic eye disease may increase.[77] This is primarily because the pathogenesis of HSK involves immunosuppression. CD4+ Th1 cells are strongly involved in the development of corneal lesions in herpes keratitis, and infiltration of CD4 cells leads to the release of cytokines, resulting in an inflammatory response that facilitates recruitment of neutrophils and macrophages.[76] Thus, changes that occur in the immune system during the natural aging process could influence the host response infection with HSV-1.[78,79]

Further studies have confirmed this rising prevalence in the older population. A retrospective review of 121 patients with clinically diagnosed HSK demonstrated that the overall mean age of patients was 64 years, with 65% of patients being 60 years or older, suggesting that this condition occurs more frequently in the elderly.[80] Additionally, patients with worse outcomes were older, presenting with poor visual acuity and larger ulcers.[80]

Clinical diagnosis of HSK is no different for older individuals, which requires clinical examination and relevant history taking.[81] Viral culture is considered gold standard for epithelial HSK but has limited use in clinical settings due to its low sensitivity. PCR performed on corneal scraping of an active lesion may be an alternative diagnostic method with greater sensitivity and rapid results.[82]

The Herpetic Eye Disease Study (HEDS) established the treatment algorithms for treating HSV keratitis.[83] Over time, additional topical and oral agents have come on the market. Although research on the treatment of HSK does not differentiate efficacy or preference between age groups, treatment strategies and principles are no different for older patients with HSV keratitis, It is widely accepted that oral anti-viral medications should be used more carefully in the elderly due to increased probability of altered pharmacodynamics.[84]

Herpes zoster, also known as shingles, is a common disease that affects healthy individuals. In the last three decades, there has been an increase in the incidence of zoster in the United States in those 40 years or older, especially among those aged 50 and older.[85] Herpes zoster is caused when the latent varicella zoster virus (VZV) is reactivated, and in 10% to 20% of cases, cranial nerve V1, the first division of the trigeminal nerve, is involved, leading to herpes zoster ophthalmicus (HZO). Complications of HZO include chronic eye inflammation in the form of keratitis or uveitis, postherpetic neuralgia (PHN), and strokes.[86] Reactivation of the VZV virus happens because of diminished cell-mediated immunity due to aging, immunosuppression, or often due to unknown factors.[85] Although aging contributes to reactivation of the virus, zoster is not solely a disease of the elderly. The most common cases of zoster, including HZO, occur in age 50s.[87] Nevertheless, timely treatment and prevention for those older than 65 are especially important due to age-related immunological changes.

Management of herpes zoster (HZ) entails promptly starting oral antiviral therapy within 72 hours of rash onset, preferably with valacyclovir or famciclovir for their enhanced bioavailability and convenience.[85] Treatment for herpes zoster ophthalmicus (HZO) has been shown to decrease ocular involvement at 6 months from roughly 50% to 30%. Antiviral therapy is particularly beneficial for individuals with HZ complications or heightened risk, such as older adults and those who are immunocompromised.[88] In 2017, a non-live, recombinant zoster vaccine (Shingrix, GlaxoSmithKline, UK) was licensed and has been in use ever since. Shingrix is the preferred shingles vaccine which is recommended by Advisory Committee on Immunization Practices due to a greater effect and stronger protection, and it is also recommended regardless of having previously received the live-attenuated VZV vaccine before (Zostavax, Merck & Co., NJ, USA).[89] A large randomized clinical trial

demonstrated that the vaccine reduces the incidence of zoster by 51% in immunocompetent individuals 60 years and older.[90] Another study supported its effectiveness, indicating that following the introduction of the live zoster vaccine in 2008, the incidence of herpes zoster ophthalmicus (HZO) declined by 5.1% among individuals aged 60 and above from 2008 to 2012.[91] Immunocompetent adults aged 50 and older are recommended to receive the zoster vaccine[92] to mitigate the risk of HZO and other zoster infections, thereby highlighting the significance of preventive measures in managing ocular viral diseases.

Fungal Keratitis

Fungal, or mycotic, keratitis is a leading cause of ocular morbidity in the world, notably in tropical and subtropical countries.[93] Mycotic Ulcer Treatment Trial (MUTT) showed that fungal keratitis cases had a larger infiltrate/scar, a slower re-epithelization rate, and a higher perforation rate than bacterial keratitis.[94] Compared to other forms of infectious keratitis, fungal keratitis carries a relatively poor prognosis due to reasons such as delayed microbiological identification, sub-optimal efficacy, and penetration of antifungal agents, morphologic pleomorphism in cultures, and a very wide spectrum of drug sensitivity with existing medications.[93] Because it is a health problem with severe consequences, it requires special attention, especially in immunocompromised populations like the elderly.

A study on fungal keratitis showed that corneal trauma is the leading risk factor, regardless of age.[95] Contact lens wear, ocular surface disorder, and ocular surgery were also contributing causes of fungal keratitis. Besides these commonly accepted risk factors, older age seems to predispose patients to fungal infections. In a study that looked at microbial keratitis at extremes of age (for example, children and elderly) compared to the general adult population, the incidence of fungal keratitis in the elderly (defined as subjects over 65 years old) were significantly higher than those in the pediatric population.[5] Filamentous fungi were one of the main causative agents among the elderly in this case series.

Another risk factor among the elderly is residence in a rural or agricultural area. A retrospective study in Sao Paulo, Brazil evaluated patients aged 60 years and older with a presumptive diagnosis of infectious keratitis to study characteristics, associated factors and causative agents of infectious keratitis in the elderly.[3] It was hypothesized that being in a rural area increased the fungal keratitis rate; prevalence of fungal infection was 56.1% in a large series of age-independent infectious keratitis from the same group and hospital. However, in urban areas, the prevalence of fungal agents was only about 0 to 7%. A different study in south India found that filamentous fungi was one of the leading causes of IK with a ratio of 31.1%, after Staphylococcus epidermidis.[96] High rates of filamentous fungi were attributed to a higher rate of agriculturally based livelihood and trauma by organic matter in more southern or tropical areas.[96]

Clinical diagnosis of fungal keratitis remains challenging, as patients present with a variety of symptoms and signs. Patients commonly experience an insidious onset and gradual progression of symptoms which include pain, watering, photophobia, foreign body sensation, and diminished visual acuity.[93] The severity of signs in fungal keratitis is less compared to that of bacterial keratitis. These signs include lid edema, conjunctival injection, chemosis, epithelial defect, and an underlying stromal infiltrate.[93] Additionally, virulent fungi like *Aspergillus* or *Fusarium* species may lead to rapid progression and corneal perforation and endophthalmitis, especially when corticosteroids are prescribed.[93] Parmar et al's study demonstrated increased incidence of central corneal ulcers and severe ulcers in older patients affected by any IK, including those of fungal etiology.[5] The central location of the infiltrate seems to be a common presentation in elderly with keratitis, as more than half of patients presented with a central rather than peripheral corneal infiltrate in Kunimoto et al's study.[96] The elderly also experienced worse visual acuity compared to both the control and pediatric groups.[5] This may be related to the elderly's tendency to delay seeking medical attention or help, even with noticeable visual changes.[96]

The first line of treatment of fungal keratitis, regardless of age, is topical natamycin.[97] MUTT I demonstrated the efficacy of natamycin over voriconazole in preventing corneal perforation and penetrating keratoplasty in smear or culture-proven fungal keratitis.[97] The MUTT II trial demonstrated no additional benefit to the addition of oral voriconazole to topical antifungal treatment.[98] However, neither MUTT nor MUTT II trials included any subjects 65 years or older. As such, treatment recommendations for the elderly based on this data would be, at best, extrapolated. Thus, despite antifungal therapy according to this algorithm, treatment may fail. Oral posaconazole has demonstrated efficacy in treating resistant cases.[99] However, oral antifungals like voriconazole and posaconazole are associated with side effects, especially in older patients, such as gastrointestinal complaints, headaches,[100] elevated liver function tests,[101]

and rarely hepatotoxicity and cardiotoxicity.[102] A case series looking at fungal keratitis in patients older than 65 years demonstrated other side effects of posaconazole like hypertensive crisis, which prompted discontinuation.[103]

Poor visual outcome is associated with older age of patient and other factors such as large and deep ulcers, pigmented ulcers, male gender, and infection with *Aspergillus* species.[104] Since older age is a factor that may reduce favorable outcomes, careful selection of treatment is essential in the elderly with fungal keratitis. These studies that looked at fungal keratitis in the elderly population used these mainstay treatments, suggesting the efficacy of these medications in those over 65, which was not directly addressed with the patient population enrolled in MUTT clinical trials.

Acanthamoeba Keratitis

Acanthamoeba keratitis (AK) is a rare protozoal infection of the cornea, and at least eight different species are known to cause this sight-threatening disease.[105] Contact lens (CL) wear is the leading risk factor for AK,[105] with relation to patient behaviors like CL contamination in the shower, swimming pools, or inconsistent CL hygiene habits.[106] Acanthamoeba is ubiquitous in the environment and has been isolated in 7% of asymptomatic CL wearer storage cases, suggesting a high prevalence of Acanthamoeba CL contamination.[106] Corneal trauma is another risk factor that facilitates invasion of microorganisms by providing a way to penetrate the eye.[106] Although AK is more likely to occur in younger patients, it can also be present in the older population (age >55 years), potentially related to systemic risks like decreased immunity, diabetes, and general health problems.[106] There is a robust host immunological response to AK in many cases, leading to severe inflammatory complications of scleritis and corneal stromal ring infiltrate.[102,107] Even relatively young and healthy patients may experience corneal transplantation and permanent vision loss.[107] Thus, careful diagnosis and treatment is especially important in the elderly who are often immunocompromised.

In a retrospective study of 259 patients diagnosed with AK, most patients were 31 to 60 years old, which accounted for 65.4% of the population.[108] Only 5.8% of the reviewed cases were patients >61 years.[108] In a study by Kunimoto et al on corneal ulcers in individuals 65 years and older in south India, only one out of 64 patients had Acanthamoeba as identified in the positive culture and was unrelated to contact lens usage.[96] In comparison, AK is responsible for about 3–5% of culture positive cases in India, which is similar to rates in North America.[96] The decreased prevalence in the elderly population may be due to infrequent contact lens wear in this age group.

Common symptoms of AK are severe pain, photophobia, and tearing.[109] These symptoms, in conjunction with diagnostic methods to visualize *Acanthamoeba* cysts or trophozoites with staining, culture, pathology, and confocal microscopy, are used to determine next steps in management.[110] A delayed time to diagnosis may lead to worse outcomes because corneal disease stage may progress and cause deep stromal keratitis or a ring infiltrate.[111] In addition to the time of diagnosis, demographics may play a role in AK outcomes. Older age predisposed patients to poor outcomes and severe inflammatory complications, likely due to altered host defenses.[107]

To date, there are no studies revealing different treatment considerations for Acanthamoeba keratitis in the elderly. Typical treatment for Acanthamoeba keratitis (AK) often involves the topical application of biguanides (eg, chlorhexidine, PHMB) and diamidines (such as propamidine isethionate, hexamidine) administered hourly.[112] However, prolonged use of chlorhexidine and PHMB can result in adverse effects like corneal ulceration and photophobia.[113] Systemic miltefosine[114] or antifungals (like neomycin, itraconazole, clotrimazole, and voriconazole)[115,116] may be used adjunctively to topical treatment. The use of topical or systemic steroids[117] may be added to reduce inflammation. Oral miltefosine, useful in refractory cases of AK,[114] is accompanied by a robust inflammatory response, necessitating the use of corticosteroids. Further studies are needed to elucidate treatment efficacy and side effects specific to the elderly population.

Conclusion

The differences in etiologic organisms of infectious keratitis (IK) in the elderly were reviewed. A summary is provided in Table 2. While many aspects of diagnosis and treatment remain consistent across age groups, older individuals often present with differences in disease severity and prognosis despite receiving the same treatment regimen. These variations stem from age-related alterations in the corneal epithelium, endothelium, and immune response. Recognizing these differences, along with the relevance of adnexal evaluation to rule out contributing factors, is crucial for early detection of infectious keratitis and preventing potential complications leading to blindness. Additionally, addressing and correcting any risk factors in aging patients is essential

Table 2 Difference Between Microbial Profile, Risk Factors, and Visual Outcomes Among Adults and Elderly (≥65 Years)

Infectious Etiology	Group	Microbial Profile	Risk Factors	Outcomes
Bacterial	Adults	Coagulase-negative Staphylococcus; Pseudomonas aeruginosa	Contact lens use, corneal trauma	Severe keratitis, potential for invasive infections
	Elderly	Gram-positive with coagulase-negative Staphylococcus; invasive Pseudomonas aeruginosa strain	Immunosuppression (diabetes, systemic drugs), corneal scarring, ocular surgery, decreased immunity	Worse vision and more severe disease on presentation, higher probability of visual impairment, increased complications
Viral	Adults	HSV-1, VZV, CMV, EBV; latent in sensory neurons	Immunosuppression, advancing age, trauma, ocular surgery, family history, sun overexposure	Mild to moderate visual impairment, responsive to antiviral treatment
	Elderly	HSV-1, VZV, CMV, EBV; higher prevalence of HSV in elderly	Immunosuppression, advancing age, trauma, ocular surgery, family history, sun overexposure	Poor visual acuity, larger ulcers, need careful use of oral antivirals
Fungal	Adults	Filamentous fungi like Aspergillus or Fusarium; commonly found in tropical/subtropical areas	Corneal trauma, contact lens wear, ocular surface disease	Slower healing, potential for severe complications
	Elderly	Filamentous fungi like Aspergillus or Fusarium; higher incidence in rural/agricultural areas	Corneal trauma, contact lens wear, ocular surface disease, rural/agricultural residency, immunocompromised state	Poor prognosis, higher perforation rates, severe central ulcers
Acanthamoeba	Adults	Acanthamoeba spp.; primarily associated with contact lens wear	Contact lens wear, corneal trauma	Mild to moderate pain, manageable with timely treatment
	Elderly	Acanthamoeba spp.; lower prevalence in elderly, but higher risk for severe outcomes in immunocompromised	Contact lens wear, corneal trauma, systemic health problems, diabetes, decreased immunity	Severe pain, potential for deep stromal keratitis, poor outcomes due to delayed diagnosis

Abbreviations: HSV, herpes simplex virus; VZV, varicella-zoster virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; spp, species.

for successful management and disease prevention. Although a potential bias exists due to the limited research specifically focusing on infectious keratitis in the elderly (Table 3), this review highlights the importance of tailored approaches for this age group to improve outcomes and preserve vision.

Table 3 Knowledge Gaps and Future Directions for Elderly Keratitis Research

Knowledge Gap	Future Direction
Risk factors specific to the elderly	More research is needed to understand the specific risk factors for infectious keratitis in the elderly, including systemic diseases and ocular surface conditions.
Progression and severity of disease in the elderly	Current studies are limited and based on case reports, limiting generalizability. More age-specific studies are required to determine the progression and severity of keratitis in the elderly.
Impact of age-related changes in corneal structure and immune response	Corneal structure and function change with age, but more research is required to determine how these changes affect risk factors, disease course, and treatment in infectious keratitis.
Treatment regimens specifically tailored for the elderly	There is a need for treatment guidelines specifically designed for the elderly, considering their unique physiological changes and potential comorbidities.

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Author Contributions

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Disclosure

The authors report no conflicts of interest in this work.

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