International Journal of Research in Medical Sciences
López DAR et al. Int J Res Med Sci. 2025 May;13(5):2255-2261
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20251345

Review Article

Acanthamoeba keratitis: a comprehensive review of pathogenesis, clinical manifestations, diagnostic challenges, and therapeutic strategies

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Received: 23 March 2025
Accepted: 18 April 2025

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ABSTRACT

Acanthamoeba keratitis (AK) is a rare but severe ocular infection caused by the protozoan parasite *Acanthamoeba spp*., which poses significant diagnostic and therapeutic challenges. This condition is frequently associated with contact lens use, corneal trauma, or exposure to contaminated water. The pathogenesis of AK involves the adhesion of *Acanthamoeba* trophozoites to the corneal epithelium, followed by invasion and subsequent tissue destruction mediated by proteolytic enzymes and cytotoxic factors. Clinically, AK presents with symptoms such as severe ocular pain, photophobia, blurred vision, and a characteristic ring-shaped corneal infiltrate. However, its nonspecific early manifestations often lead to misdiagnosis or delayed treatment, exacerbating the risk of corneal perforation and permanent visual impairment. Diagnosis relies on a combination of clinical suspicion, microbiological techniques (e.g., corneal scrapings, culture, and confocal microscopy), and molecular methods such as PCR. Current therapeutic approaches include biguanides (e.g., polyhexamethylene biguanide), diamidines (e.g., propamidine isethionate), and adjunctive corticosteroids, although treatment resistance and recurrence remain significant concerns. This review aims to provide an in-depth analysis of the epidemiology, pathophysiology, clinical features, diagnostic modalities, and emerging therapeutic options for AK, emphasizing the need for early recognition and multidisciplinary management to improve patient outcomes.

Keywords: Acanthamoeba keratitis, Ocular infection, Contact lens-related keratitis, Corneal infiltrate, Protozoan pathogens, Diagnostic challenges, Antimicrobial therapy, Corneal transplantation

INTRODUCTION

Acanthamoeba keratitis (AK) is a vision-threatening corneal infection caused by free-living protozoa of the genus *Acanthamoeba*. First described in the early 1970s, AK has since emerged as a significant cause of infectious keratitis, particularly among contact lens wearers. The incidence of AK has risen in recent decades, paralleling the increasing global use of contact lenses and exposure to contaminated water sources. Despite its rarity, AK is associated with substantial morbidity due to its aggressive clinical course, diagnostic complexities, and limited therapeutic options.[1,2]

The pathogenesis of AK involves a multifactorial process initiated by the adherence of *Acanthamoeba* trophozoites to the corneal epithelium, facilitated by mannose-binding proteins and other surface ligands. Once attached, the parasite invades the corneal stroma, releasing proteases such as elastases and serine proteases that degrade

extracellular matrix components and induce inflammatory responses. This results in progressive corneal ulceration, stromal necrosis, and, in advanced cases, perforation.[1-3]

Clinically, AK is characterized by severe ocular pain disproportionate to clinical findings, photophobia, redness, and blurred vision. Early stages of the disease often mimic other forms of microbial keratitis, leading to diagnostic delays and inappropriate treatment. Advanced imaging techniques, such as *in vivo* confocal microscopy, and molecular diagnostics, including polymerase chain reaction (PCR), have improved diagnostic accuracy. However, challenges remain in differentiating AK from bacterial, fungal, or viral keratitis.[4,5]

Treatment of AK is protracted and often complicated by the parasite's resistance to conventional antimicrobial agents. Current regimens typically involve a combination of topical biguanides and diamidines, with adjunctive corticosteroids used cautiously to modulate inflammation. In refractory cases, surgical interventions such as corneal transplantation may be necessary, though the risk of recurrence remains high.[4,5]

This article provides a comprehensive overview of AK, focusing on its epidemiology, molecular mechanisms, clinical presentation, diagnostic approaches, and therapeutic advancements. By synthesizing current evidence and highlighting areas for future research, this review aims to enhance the understanding of AK and improve clinical outcomes for affected patients.[5,6]

EPIDEMIOLOGY OF AK

AK is a rare but increasingly recognized ocular infection with significant public health implications. Epidemiology of AK is characterized by its association with specific risk factors, geographic distribution, and temporal trends, which collectively underscore the importance of understanding its prevalence and determinants.[6,7]

Globally, the incidence of AK varies widely, with higher rates reported in developed countries, particularly in regions with widespread contact lens use. In the United States and Europe, AK accounts for approximately 1-2% of all cases of microbial keratitis, though this figure may be underestimated due to diagnostic challenges and underreporting. The annual incidence in the U.S. is estimated to be 1-2 cases per million contact lens wearers, while in the United Kingdom, the incidence has been reported to range from 1.4 to 2.0 cases per million population. Notably, the incidence of AK has shown an upward trend over the past few decades, coinciding with the growing popularity of contact lenses and changes in lens hygiene practices.[6]

Contact lens wear remains the most significant risk factor for AK, contributing to approximately 85-90% of cases. Improper lens care, including the use of tap water for rinsing or storing lenses, failure to disinfect lenses adequately, and extended wear, significantly increases the risk of infection. Soft contact lenses, in particular, have been implicated due to their higher water content and greater propensity to harbor pathogens. Additionally, corneal trauma, exposure to contaminated water (e.g., swimming pools, hot tubs/freshwater sources), and ocular surface diseases are recognized predisposing factors.[6]

Geographically, AK exhibits a higher prevalence in temperate climates, where *Acanthamoeba* species are more commonly found in soil and water. However, cases have been reported worldwide, including in tropical and subtropical regions, reflecting the ubiquitous nature of the pathogen. Seasonal variations have also been observed, with a higher incidence during warmer months, likely due to increased recreational water activities.[7]

Demographically, AK predominantly affects young to middle-aged adults, with a mean age of onset ranging from 25-40 years. There is no significant gender predilection, although some studies suggest slight female predominance, possibly reflecting higher contact lens use among women. Socioeconomic factors, such as access to clean water and healthcare resources, may also influence risk and outcomes of AK, particularly in low-resource settings.[7]

The emergence of AK as a public health concern has been further exacerbated by the COVID-19 pandemic, during which changes in hygiene practices and increased use of homemade saline solutions for contact lens care have been reported. This highlights the need for ongoing public health initiatives to educate contact lens users about proper hygiene and risks associated with nonsterile water exposure.[7]

In conclusion, the epidemiology of AK is shaped by a complex interplay of behavioral, environmental, and microbiological factors. Understanding these determinants is crucial for developing targeted prevention strategies, improving diagnostic accuracy, and optimizing therapeutic outcomes. Continued surveillance and research are essential to address the evolving burden of AK and mitigate its impact on global eye health.[8]

CLINICAL MANIFESTATIONS OF AK

AK is a severe and potentially sight-threatening corneal infection characterized by a diverse array of clinical manifestations that often pose diagnostic challenges due to their nonspecific nature in the early stages of the disease. The clinical presentation of AK typically evolves through distinct phases, each marked by progressive symptomatology and corneal pathology, reflecting the underlying pathogenic mechanisms of *Acanthamoeba* invasion and host immune response.[8]

In the initial stage of AK, patients often report symptoms that are nonspecific and may mimic other forms of microbial keratitis, such as bacterial, fungal/viral

infections. Early symptoms include ocular discomfort, foreign body sensation, mild to moderate pain, photophobia, epiphora (excessive tearing), and blurred vision. These symptoms are frequently disproportionate to the clinical findings on slit-lamp examination, which may reveal subtle corneal epithelial irregularities, punctate epithelial erosions, or mild conjunctival injection. This discrepancy between symptoms and signs is a hallmark of early AK and often leads to delayed diagnosis/ misdiagnosis.[8]

As the infection progresses, clinical picture becomes more pronounced and characteristic. The hallmark feature of AK is severe, unrelenting ocular pain, which is often described as disproportionate to the degree of corneal involvement and is thought to result from radial keratoneuritis, an inflammation of corneal nerves caused by *Acanthamoeba* invasion. Slit-lamp examination at this stage may reveal a stromal infiltrate, which can initially appear as a focal, grayish-white opacity. Over time, the infiltrate may coalesce to form a ring-shaped ulcer, a pathognomonic finding in AK, although this is not present in all cases. The ring infiltrate is caused by the accumulation of inflammatory cells and necrotic debris in the mid-stroma and is often accompanied by surrounding corneal edema.[8,9]

In addition to the ring infiltrate, other corneal findings may include epithelial and subepithelial opacities, pseudo-dendrites (which can be mistaken for herpes simplex virus keratitis), and radial perineural infiltrates. The latter are linear, branching opacities that radiate from the central cornea and correspond to the path of the corneal nerves. These infiltrates are highly suggestive of AK and can aid in differentiating it from other forms of keratitis.[8-10]

In advanced stages of AK, the infection can lead to profound corneal thinning, ulceration, and even perforation, particularly if diagnosis and treatment are delayed. Patients may develop anterior uveitis, hypopyon (accumulation of inflammatory cells in the anterior chamber), and scleritis, reflecting the extension of inflammation beyond the cornea. Severe cases may also result in secondary bacterial or fungal infections, further complicating the clinical course and management.[11]

Chronic or recurrent AK is characterized by persistent inflammation, stromal scarring, and neovascularization, which can lead to significant visual impairment or blindness. In some cases, the infection may become refractory to medical therapy, necessitating surgical interventions such as corneal transplantation. However, even after surgical treatment, risk of recurrence remains high due to the resilient nature of *Acanthamoeba* cysts.[11]

The clinical manifestations of AK are further influenced by host factors, such as immune status and preexisting ocular conditions, as well as the virulence of the infecting *Acanthamoeba* strain. Immunocompromised individuals, for example, may experience a more aggressive disease course with rapid progression to corneal perforation.[11]

In summary, the clinical manifestations of AK are diverse and evolve over time, ranging from nonspecific early symptoms to characteristic findings such as radial keratoneuritis, ring infiltrates, and stromal ulceration. A high index of suspicion, combined with careful clinical evaluation and appropriate diagnostic testing, is essential for timely diagnosis and management. Understanding the spectrum of clinical presentations is crucial for optimizing outcomes and preventing the devastating sequelae of this challenging ocular infection.[11]

DIAGNOSTIC METHODS FOR AK

Diagnosis of AK represents a significant clinical challenge due to its nonspecific early symptoms, overlapping features with other forms of microbial keratitis, and the inherent difficulties in detecting the causative organism. A definitive diagnosis of AK requires multifaceted approach that integrates clinical suspicion, advanced imaging techniques, microbiological assays, and molecular diagnostics. This section provides comprehensive overview of diagnostic modalities employed in evaluation of AK, emphasizing their respective advantages, limitations, and roles in diagnostic algorithm.[12]

Clinical evaluation and slit-lamp examination

The diagnostic process begins with a thorough clinical history and slit-lamp examination. Key historical features include contact lens use, exposure to contaminated water, and a history of corneal trauma. Slit-lamp findings such as radial keratoneuritis, ring-shaped stromal infiltrates, pseudodendrites, and perineural infiltrates are highly suggestive of AK, although these features may not be present in early stages. The presence of severe ocular pain disproportionate to clinical findings should raise suspicion for AK, even in the absence of characteristic signs.[12]

IN VIVO CONFOCAL MICROSCOPY

In vivo confocal microscopy (IVCM) has emerged as a valuable noninvasive tool for the diagnosis of AK. IVCM allows for real-time, high-resolution imaging of the corneal layers at the cellular level, enabling the visualization of *Acanthamoeba* cysts and trophozoites. Cysts typically appear as hyperreflective, double-walled, round or oval structures, while trophozoites may exhibit a more irregular, hyperreflective morphology. IVCM is particularly useful in cases where microbiological testing is inconclusive or when early diagnosis is critical to prevent disease progression. However, its utility may be limited by operator expertise and the availability of specialized equipment.[13]

Microbiological techniques

Microbiological testing remains the cornerstone of AK diagnosis and involves the collection of corneal scrapings or biopsies for direct examination and culture.

Direct microscopy

Corneal scrapings are stained with calcofluor white, a fluorescent dye that binds to the polysaccharide components of *Acanthamoeba* cysts, rendering them visible under ultraviolet light. Other stains, such as Gram, Giemsa, and periodic acid-Schiff (PAS), may also be used, although they are less specific. Direct microscopy provides rapid results but requires expertise in interpreting morphological features.[14]

Culture

Culture remains the gold standard for AK diagnosis. Corneal specimens are inoculated onto non-nutrient agar plates overlaid with *Escherichia coli* or other bacteria, which serve as a food source for *Acanthamoeba*. Trophozoites and cysts can be observed within 48 to 72 hours, although culture sensitivity may be reduced in cases of prior antimicrobial therapy. Culture also allows for species identification and susceptibility testing, which can guide treatment.[14]

Molecular diagnostics

Molecular techniques, particularly polymerase chain reaction (PCR), have revolutionized the diagnosis of AK by offering high sensitivity and specificity. PCR targets conserved regions of *Acanthamoeba* DNA, such as the 18S rRNA gene, and can detect the organism even in cases with low microbial load or prior treatment. Real-time PCR (qPCR) further enhances diagnostic accuracy by providing quantitative results and reducing turnaround time. However, PCR requires specialized laboratory infrastructure and is susceptible to contamination, which can lead to false-positive results.[15]

Histopathological examination

In cases where corneal transplantation is performed, histopathological examination of the excised tissue can provide definitive evidence of AK. Hematoxylin and eosin (H and E) staining may reveal cysts and trophozoites within the corneal stroma, while special stains such as PAS and Gomori methenamine silver (GMS) can enhance their visibility. Histopathology is particularly useful in chronic or refractory cases but is not applicable for early diagnosis.[15]

ANCILLARY TESTS

Anterior segment optical coherence tomography (AS-OCT)

AS-OCT can provide detailed cross-sectional images of the cornea, aiding in the assessment of stromal involvement, corneal thinning, and ulceration. While not specific for AK, AS-OCT can complement other diagnostic modalities by providing structural information.[15]

Serological testing

Serological assays for *Acanthamoeba*-specific antibodies have limited utility in AK diagnosis due to the localized nature of the infection and the lack of a systemic immune response in most cases.[15]

CHALLENGES AND FUTURE DIRECTIONS

Despite advances in diagnostic techniques, challenges remain in the timely and accurate diagnosis of AK. These include the low sensitivity of conventional methods, the need for specialized equipment and expertise, and the potential for false-negative results in treated or early-stage cases. Emerging technologies, such as next-generation sequencing (NGS) and artificial intelligence (AI)-assisted image analysis, hold promise for improving diagnostic accuracy and efficiency.[15]

The diagnosis of AK requires a multimodal approach that combines clinical evaluation, advanced imaging, microbiological testing, and molecular diagnostics. Early and accurate diagnosis is critical to prevent disease progression and improve patient outcomes. Continued research and innovation in diagnostic methods are essential to address the challenges posed by this complex and potentially devastating ocular infection.[15]

THERAPEUTIC METHODS FOR AK

The management of AK is a complex and evolving challenge in ophthalmology, requiring a multifaceted therapeutic approach to address both the infectious agent and the associated inflammatory response. The treatment of AK is protracted, often spanning several months, and is complicated by the organism's dual life cycle, consisting of resistant cysts and metabolically active trophozoites, as well as the potential for drug resistance and recurrence. This section provides a comprehensive overview of the therapeutic strategies employed in the management of AK, encompassing antimicrobial therapy, anti-inflammatory agents, and surgical interventions, while highlighting emerging treatments and future directions.[15]

ANTIMICROBIAL THERAPY

The cornerstone of AK treatment is the use of topical antimicrobial agents that target both trophozoites and cysts. These agents are typically administered as intensive hourly regimens initially, followed by gradual tapering as clinical improvement is observed.[15]

Biguanides

Polyhexamethylene biguanide (PHMB): PHMB, a cationic polymer, is one of the most commonly used agents for AK. It disrupts the cell membrane of *Acanthamoeba*, leading to cell lysis. PHMB is effective against both trophozoites and cysts and is typically used at concentrations of 0.02% to 0.06%.[15]

Chlorhexidine: Another biguanide, chlorhexidine, is used at concentrations of 0.02% to 0.2%. It exhibits similar mechanisms of action to PHMB and is often used in combination with other agents to enhance efficacy.[15]

Diamidines

Propamidine isethionate (Brolene): This diamidine derivative is effective against *Acanthamoeba* trophozoites and is often used in combination with biguanides. It is typically administered as a 0.1% solution.[15]

Hexamidine: Another diamidine, hexamidine, is used in some regions and has shown efficacy against both trophozoites and cysts.[15]

Azoles

Voriconazole: This broad-spectrum triazole antifungal agent has shown promise in the treatment of AK, particularly in cases resistant to conventional therapy. It can be administered topically or systemically, depending on the severity of the infection.[15]

Aminoglycosides

Neomycin and paromomycin: These have been used as adjunctive therapies in AK, although their efficacy is limited compared to biguanides and diamidines.[15]

Combination therapy: Given the potential for resistance and the need to target both life stages of *Acanthamoeba*, combination therapy is often employed. Common regimens include PHMB or chlorhexidine combined with propamidine isethionate or voriconazole.[15]

ANTI-INFLAMMATORY THERAPY

The intense inflammatory response associated with AK can lead to corneal scarring, neovascularization, and stromal melting. Corticosteroids are sometimes used adjunctively to modulate inflammation, but their use remains controversial due to the risk of exacerbating the infection. When used, corticosteroids should be initiated only after effective antimicrobial therapy has been established and should be closely monitored.[15]

Surgical interventions

In cases where medical therapy fails or complications arise, surgical interventions may be necessary.[15]

Corneal debridement: Mechanical debridement of the infected corneal epithelium can reduce the microbial load and enhance the penetration of topical agents.[15]

Corneal transplantation

Penetrating keratoplasty (PKP): In advanced cases with corneal perforation or severe scarring, PKP may be required to restore corneal integrity and visual function. However, the risk of recurrence in the graft is significant, and postoperative antimicrobial therapy is essential.

Deep anterior lamellar keratoplasty (DALK): DALK is preferred in cases where the endothelium is spared, as it reduces the risk of graft rejection compared to PKP.[15]

EMERGING THERAPIES

Photodynamic therapy (PDT)

PDT involves use of photosensitizing agents activated by light to generate reactive oxygen species that kill *Acanthamoeba*. Early studies have shown promise, but further research is needed to establish its efficacy and safety.[15]

Nanotechnology

Nanoparticle-based drug delivery systems are being explored to enhance the penetration and efficacy of antimicrobial agents in the cornea. These systems can provide sustained release and targeted delivery, potentially reducing treatment duration and side effects.[15]

Immunotherapy

Research into immunomodulatory therapies, such as monoclonal antibodies and cytokine inhibitors, aims to enhance the host immune response while minimizing tissue damage.[15]

Supportive care

Supportive measures, such as lubricating eye drops, bandage contact lenses, and pain management, play a crucial role in alleviating symptoms and promoting corneal healing. Patient education on proper contact lens hygiene and follow-up care is essential to prevent recurrence.[15]

The treatment of AK is fraught with challenges, including drug resistance, prolonged treatment duration, and the risk of recurrence. Future research should focus on developing novel antimicrobial agents, optimizing drug delivery systems, and exploring targeted therapies that address both the infectious and inflammatory components of AK.[16]

The management of AK requires a comprehensive and individualized approach that combines antimicrobial therapy, anti-inflammatory agents, and surgical interventions when necessary.

Early diagnosis and aggressive treatment are critical to achieving favorable outcomes and preserving visual function. Continued research and innovation in therapeutic strategies are essential to address the complexities of this challenging ocular infection.[16]

CONCLUSION

AK represents a formidable challenge in the field of ophthalmology, characterized by its complex pathogenesis, diagnostic intricacies, and therapeutic difficulties. This severe corneal infection, caused by the free-living protozoan *Acanthamoeba spp.*, is associated with significant morbidity and the potential for permanent visual impairment if not promptly and effectively managed. Despite advances in diagnostic and therapeutic modalities, AK continues to pose substantial clinical and public health concerns, particularly among contact lens wearers and individuals exposed to contaminated water sources.

The epidemiology of AK underscores the importance of preventive measures, particularly in the context of contact lens use. Public health initiatives aimed at educating contact lens users about proper hygiene practices, such as avoiding the use of tap water for lens cleaning and adhering to recommended disinfection protocols, are critical to reducing the incidence of this devastating infection. Additionally, heightened awareness among healthcare providers regarding the early signs and symptoms of AK is essential to facilitate timely diagnosis and intervention.

The clinical manifestations of AK, ranging from nonspecific early symptoms to characteristic findings such as radial keratoneuritis and ring-shaped stromal infiltrates, highlight the need for a high index of suspicion in at-risk populations. Advanced diagnostic tools, including *in vivo* confocal microscopy (IVCM) and molecular techniques such as polymerase chain reaction (PCR), have significantly improved diagnostic accuracy. However, challenges remain in differentiating AK from other forms of microbial keratitis, particularly in the early stages of the disease.

Therapeutic management of AK is multifaceted and often prolonged, requiring a combination of topical antimicrobial agents, such as biguanides and diamidines, to target both trophozoites and cysts. Adjunctive anti-inflammatory therapy and surgical interventions, including corneal transplantation, may be necessary in refractory or advanced cases. Despite these treatment options, the risk of recurrence and drug resistance remains a significant concern, underscoring the need for continued research into novel therapeutic strategies.

Emerging therapies, such as photodynamic therapy (PDT), nanotechnology-based drug delivery systems, and immunomodulatory approaches, hold promise for improving treatment outcomes and reducing the burden of AK. Furthermore, advancements in diagnostic technologies, including AI-assisted imaging and NGS, may enhance early detection and personalized management of this condition.

In conclusion, Acanthamoeba keratitis is a complex and potentially devastating ocular infection that requires a multidisciplinary approach to diagnosis, treatment, and prevention. Early recognition, aggressive antimicrobial therapy, and ongoing patient education are essential to optimizing outcomes and preserving visual function. Continued research and innovation in both diagnostic and therapeutic modalities are crucial to addressing the challenges posed by AK and improving the quality of life for affected patients. By fostering collaboration among clinicians, researchers, and public health professionals, we can advance our understanding of this condition and develop more effective strategies to combat its impact on global eye health.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: López DAR, López DES, Ruiz IAR, Martínez ALM, Campos BMMM, Flores LVS. Acanthamoeba keratitis: a comprehensive review of pathogenesis, clinical manifestations, diagnostic challenges, and therapeutic strategies. Int J Res Med Sci 2025;13:2255-61.