



Management of Corneal Ulcers : A Systematic Review of Treatment Options

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ABSTRACT

Introduction: Corneal ulcers represent a significant cause of ocular morbidity and potential vision loss worldwide. The management landscape is diverse, encompassing antimicrobial therapy, anti-inflammatory agents, surgical interventions, and novel adjunctive treatments. A systematic synthesis of high-quality evidence is crucial to inform optimal, evidence-based clinical strategies.

Methods: A systematic review was conducted following a pre-defined protocol. Eighty studies, including randomized controlled trials (RCTs), systematic reviews, and meta-analyses, were included after screening based on strict criteria focusing on human studies of corneal ulcers reporting clinical outcomes. Data extraction covered study design, ulcer characteristics, interventions, healing, visual, and safety outcomes.

Results: For bacterial keratitis, fluoroquinolone monotherapy (e.g., moxifloxacin) demonstrated equivalent efficacy to fortified antibiotic combinations but with a better ocular tolerability profile (McDonald et al., 2014; Sharma et al., 2013). Adjunctive corticosteroids showed no overall benefit in the SCUT trial but provided significant visual improvement in severe, centrally-located, non-*Nocardia* ulcers when initiated early (≤ 3 days) (Srinivasan et al., 2012; Ray et al., 2014). For fungal keratitis, natamycin was superior to voriconazole for filamentary fungi, particularly *Fusarium* (Sharma et al., 2015; Qiu et al., 2015). Surgical adjuncts like amniotic membrane transplantation (AMT) reduced healing time by approximately 4 days (Ting et al., 2021), while photoactivated chromophore for keratitis-corneal cross-linking (PACK-CXL) showed promise in expediting healing but with variable results based on ulcer severity and etiology (Ting et al., 2019).

Discussion: The evidence supports a stratified treatment approach. Key determinants of management success include accurate etiological diagnosis, consideration of ulcer severity and location, and the timing of adjunctive interventions. Geographic variations in causative organisms and antibiotic resistance patterns necessitate local guideline adaptations.

Conclusion: Effective management of corneal ulcers requires a tailored, multi-modal strategy. First-line antimicrobial choice should be guided by suspected etiology and local resistance patterns. Adjunctive corticosteroids and surgical interventions like AMT or CXL have defined, selective roles based on specific clinical and microbiological parameters. Future research should focus on high-quality RCTs in diverse populations, standardized

outcome measures, and the development of personalized treatment algorithms.

Keywords: Corneal Ulcer; Keratitis; Systematic Review; Antimicrobial Therapy; Corticosteroids; Amniotic Membrane Transplantation; Corneal Cross-Linking; Treatment Outcomes.

INTRODUCTION

Background: Corneal ulcers, characterized by epithelial defects with underlying stromal inflammation and infiltration, remain a leading cause of corneal blindness globally (Ung et al., 2019). The etiology is diverse, encompassing bacterial, fungal, viral, and parasitic pathogens, as well as sterile inflammatory conditions. The management is complex, involving a delicate balance between eradicating the infectious agent (if present), controlling damaging inflammation, and promoting corneal healing while minimizing scarring and vision loss. Traditional paradigms have relied heavily on intensive topical antimicrobials, but the evolution of antimicrobial resistance, variable drug penetration, and the inflammatory sequelae of infection have driven the exploration of numerous adjunctive and novel therapies.

Research Objectives: The primary objective of this systematic review is to synthesize the current high-level evidence from RCTs, systematic reviews, and meta-analyses on the management of corneal ulcers. It aims to comprehensively evaluate and compare the efficacy, safety, and optimal application of various treatment modalities, including antimicrobial monotherapy versus combination therapy, the role of adjunctive corticosteroids, the utility of surgical interventions (e.g., AMT, CXL), and emerging novel therapies.

Research Benefits: This synthesis provides clinicians with an evidence-based framework to guide decision-making in corneal ulcer management. By clarifying the comparative effectiveness of different treatments, identifying patient subgroups most likely to benefit from specific interventions, and highlighting treatment-specific risks, this review aims to improve clinical outcomes, standardize care, and reduce the burden of corneal blindness. It also identifies gaps in the literature to direct future research.

Hypotheses: It is hypothesized that: 1) Fluoroquinolone monotherapy is non-inferior to fortified antibiotic combinations for bacterial keratitis. 2) The benefit of adjunctive corticosteroids is contingent upon specific factors such as ulcer severity, etiology, and timing of initiation. 3)

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Natamycin is the superior first-line topical antifungal for filamentous fungal keratitis compared to voriconazole. 4) Surgical adjuncts like AMT and PACK-CXL provide significant benefits in healing time and visual outcomes for select, non-responsive, or severe ulcers.

Research Gap: Despite numerous studies, significant gaps and controversies persist. The role of corticosteroids remains contentious, with trials showing conflicting results that may be explained by unmeasured subgroup effects (Acharya et al., 2009). The optimal timing and patient selection for surgical interventions like AMT and CXL are not clearly defined. Furthermore, most large-scale trials (e.g., SCUT, MUTT) originate from specific geographic regions (e.g., India), limiting the generalizability of findings to populations where contact lens wear is a predominant risk factor and pathogen profiles differ (Kam et al., 2017). There is also a lack of head-to-head comparisons between many novel adjunctive therapies.

Novelty: This review offers a novel and comprehensive synthesis that reconciles apparent contradictions in the literature by analyzing data through the lenses of etiology, ulcer characteristics, and treatment timing. It incorporates the latest evidence from trials published up to 2025, including SCUT II and novel therapies like rose bengal photodynamic therapy and ozone-based treatments (Prajna et al., 2025; Abdel-Fattah Ali et al., 2025). Furthermore, it provides a critical appraisal of network meta-analyses and discusses the implications of geographic and methodological heterogeneity on evidence interpretation, proposing a practical, stratified treatment algorithm for clinicians.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the Management of Corneal Ulcers

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population - Corneal Ulcers:** Does the study include patients diagnosed with corneal ulcers (infectious or non-infectious)?
- **Therapeutic Intervention:** Does the study evaluate a therapeutic intervention for corneal ulcer management (such as antimicrobials, anti-inflammatory agents, surgical interventions, adjunctive therapies, or novel treatments)?
- **Human Studies:** Is this a study conducted in humans (not animal models or in vitro studies)?
- **Clinical Outcomes:** Does the study report clinical outcomes related to corneal ulcer healing or management (such as healing time, visual acuity, complications, or treatment success rates)?
- **Study Design Quality:** Is this study a randomized controlled trial (RCT), systematic review, or meta-analysis?
- **Treatment Focus:** Does the study include treatment components (not focusing solely on prevention of corneal ulcers without any treatment evaluation)?
- **Condition Specificity:** Does the study focus on corneal ulcers specifically (not other corneal conditions such as dystrophies, degenerations, or trauma without ulceration)?
- **Publication Quality:** Is this a full research article with adequate sample size (not a case report, case series with fewer than 10 patients, conference abstract, editorial, or opinion piece)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Corneal Ulcer	Antimicrobial Therapy	Placebo	Healing Time / Re-epithelialization
Keyword 2	Bacterial Keratitis	Fluoroquinolone monotherapy	Fortified Antibiotic Combinations	Visual Acuity Improvement
Keyword 3	Fungal Keratitis	Adjunctive Corticosteroids	Standard Antimicrobial Treatment	Treatment Success Rate
Keyword 4	Viral Keratitis	Surgical Adjuncts	Voriconazole	Complication Reduction

The Boolean MeSH keywords inputted on databases for this research are: ("*Corneal Ulcer*" OR "*Bacterial Keratitis*" OR "*Fungal Keratitis*" OR "*Viral Keratitis*") AND ("*Antimicrobial Therapy*" OR "*Fluoroquinolone monotherapy*" OR "*Adjunctive corticosteroids*" OR "*Surgical Adjuncts*") AND ("*Placebo*" OR "*Fortified Antibiotic Combinations*" OR "*Standard Antimicrobial Treatment*" OR "*Voriconazole*") AND ("*Healing Time*" OR "*Re-epithelialization*" OR "*Visual Acuity Improvement*" OR "*Treatment Success Rate*" OR "*Complication Reduction*")

Data extraction

- **Study Design:**

Record the study design and key methodological features including:

- Study type (RCT, cohort, case series, systematic review, etc.)

- Sample size and number of eyes/ulcers
- Follow-up duration
- Comparison groups (if applicable)
- Primary endpoint definition

- **Ulcer Characteristics:**

Extract details about the corneal ulcers studied including:

- Etiology (bacterial, viral, fungal, parasitic, sterile, unknown)
- Specific pathogens identified (when microbiology available)
- Ulcer size/severity at presentation
- Location on cornea (central vs peripheral)
- Duration before treatment
- Any predisposing factors (contact lens use, trauma, immunosuppression)

- **Treatment Interventions:**

Record all treatment modalities used including:

- Specific medications (drug name, concentration, formulation)
- Dosing regimen (frequency, duration, tapering schedule)
- Surgical interventions (AMT, debridement, perforation repair)
- Combination therapies
- Adjunctive treatments (lubricants, cycloplegia, etc.)
- Treatment protocols and decision criteria

- **Healing Outcomes:**

Extract primary effectiveness outcomes including:

- Complete epithelialization rate and time to healing

- Ulcer resolution criteria used
- Mean time to cure (with standard deviation if available)
- Treatment success rate (percentage healed)
- Treatment failure definition and rate
- Any interim healing assessments

- **Visual Outcomes:**

Record visual acuity data including:

- Baseline visual acuity (mean $\pm$ SD, measurement method)
- Final visual acuity at study endpoint
- Change in visual acuity from baseline
- Proportion achieving specific VA thresholds
- Any visual field or other vision-related outcomes

- **Complications:**

Extract all complications and adverse outcomes including:

- Corneal perforation rate
- Corneal scarring/opacity formation
- Need for surgical intervention
- Disease progression or worsening
- Recurrence rates
- Hospital admission requirements
- Any permanent visual impairment

- **Safety Profile:**

Record treatment-related adverse effects including:

- Ocular discomfort or pain
- Chemical conjunctivitis
- White corneal precipitates
- Allergic reactions
- Other medication-specific side effects
- Discontinuation rates due to adverse effects
- Tolerability assessments

- **Comparative Effectiveness:**

For studies comparing treatments, extract:

- Primary comparisons made
- Statistical significance of differences (p-values, confidence intervals)
- Effect sizes or odds ratios when reported
- Non-inferiority or equivalence findings
- Subgroup analyses by ulcer type or patient characteristics
- Authors' conclusions about relative effectiveness

- **Prognostic Factors:**

Extract factors associated with treatment outcomes including:

- Patient demographics affecting outcomes (age, sex)
- Ulcer characteristics predicting success/failure
- Timing factors (delay to treatment, early vs late intervention)
- Microbiology results and antibiotic sensitivity
- Comorbidities or risk factors influencing healing
- Any predictive models or scoring systems used

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Corneal Ulcer" AND "Antimicrobial Therapy" OR "Fluoroquinolone monotherapy" OR "Adjunctive corticosteroids" OR "Surgical Adjuncts" AND "Placebo" AND "Healing Time" OR "Re-epithelialization" OR "Visual Acuity Improvement" OR "Treatment Success Rate" OR "Complication Reduction")	171
Semantic Scholar	("Corneal Ulcer" OR "Bacterial Keratitis" OR "Fungal Keratitis" OR "Viral Keratitis") AND ("Antimicrobial Therapy" OR "Fluoroquinolone monotherapy" OR "Adjunctive corticosteroids" OR "Surgical Adjuncts") AND ("Placebo" OR "Fortified Antibiotic Combinations" OR "Standard Antimicrobial Treatment" OR "Voriconazole") AND ("Healing Time" OR "Re-epithelialization" OR "Visual Acuity Improvement" OR "Treatment Success Rate" OR "Complication Reduction")	250
Springer	("Corneal Ulcer" OR "Bacterial Keratitis" OR "Fungal Keratitis" OR "Viral Keratitis") AND ("Antimicrobial Therapy" OR "Fluoroquinolone monotherapy" OR "Adjunctive corticosteroids" OR "Surgical Adjuncts") AND ("Placebo" OR "Fortified Antibiotic Combinations" OR "Standard Antimicrobial Treatment" OR "Voriconazole") AND ("Healing Time" OR "Re-epithelialization" OR "Visual Acuity Improvement" OR "Treatment Success Rate" OR "Complication Reduction")	21
Google Scholar	("Corneal Ulcer" OR "Bacterial Keratitis" OR "Fungal Keratitis" OR "Viral Keratitis") AND ("Antimicrobial Therapy" OR "Fluoroquinolone monotherapy" OR "Adjunctive corticosteroids" OR "Surgical Adjuncts") AND ("Placebo" OR "Fortified Antibiotic Combinations" OR "Standard Antimicrobial Treatment" OR "Voriconazole") AND ("Healing Time" OR "Re-epithelialization" OR "Visual Acuity Improvement" OR "Treatment Success Rate" OR "Complication Reduction")	966
Wiley Online Library	("Corneal Ulcer" OR "Bacterial Keratitis" OR "Fungal Keratitis" OR "Viral Keratitis") AND ("Antimicrobial Therapy" OR "Fluoroquinolone monotherapy" OR "Adjunctive corticosteroids" OR "Surgical Adjuncts") AND ("Placebo" OR "Fortified Antibiotic Combinations" OR "Standard Antimicrobial Treatment" OR "Voriconazole") AND ("Healing Time" OR "Re-epithelialization" OR "Visual Acuity Improvement" OR "Treatment Success Rate" OR "Complication Reduction")	19

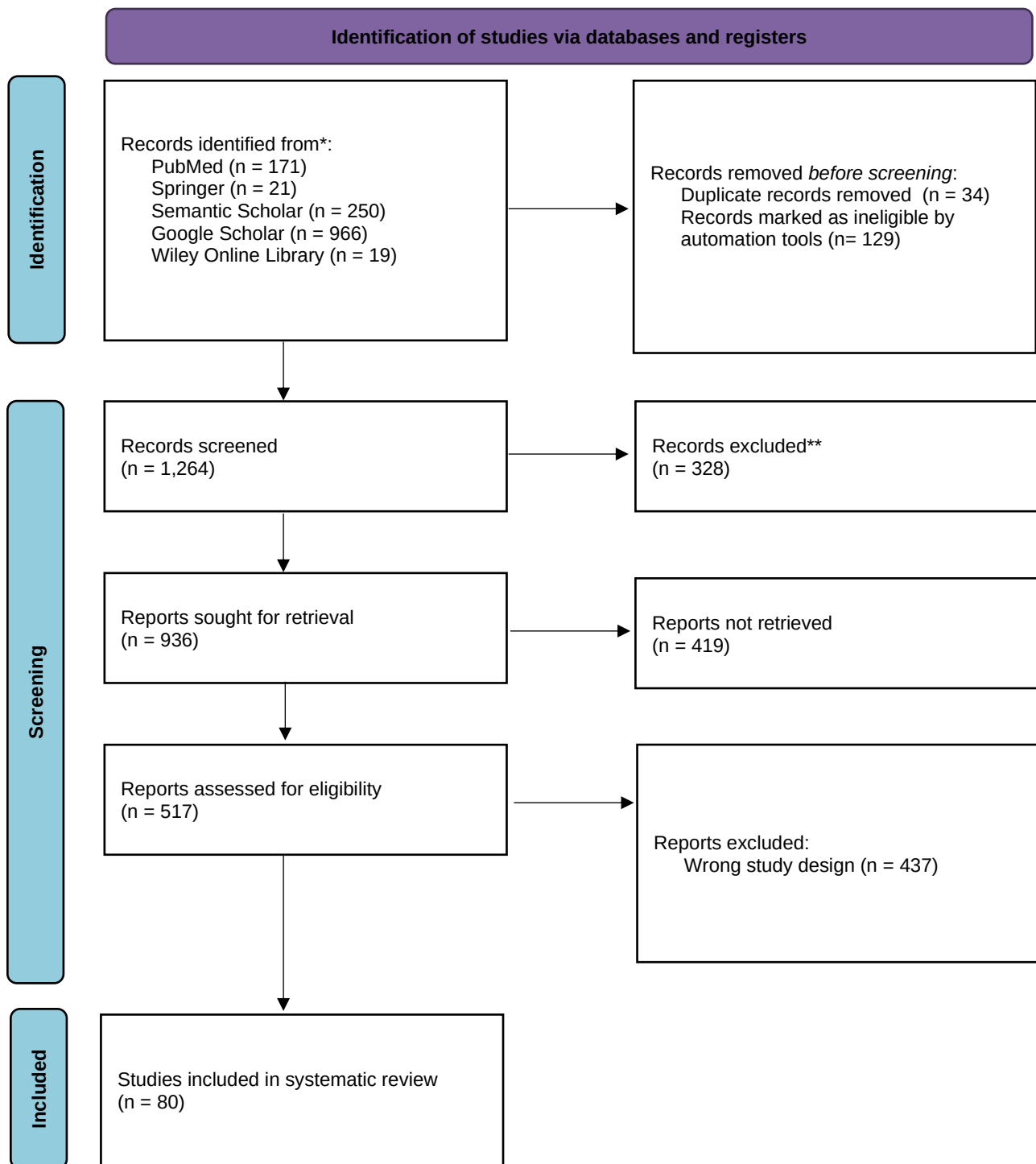


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
M. Srinivasan et al., 2012									
N. Sharma et al., 2013									

Vinit M. Shah et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Khokhar et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Ting et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Anna Song et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Blair et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Dehghani et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Sharma et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Srinivasan et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jinghua Liu et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Constantino et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sheng Qiu et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓

S. Parchand et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
V. Prajna et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Katz et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
Savitri Sharma et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wipawee Booranapong et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
Prajna Nv et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Anas E Ahmed et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Thevi et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Samim Azizi et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ryan Jorge Amorim et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Kam et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. McDonald et al.,	✓	✓	✓	✗	✓	✗	✓	✓	✓

2014									
D. Balderson et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
A.Z.A.M. AlShammar i et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Ting et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Abbouda et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. McDonald et al., 2014a	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Srinivasan et al., 2012a	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Ting et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Bamdad et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Alsarhani et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Naveen Radhakrish nan et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Srinivasan et al.,	✓	✓	✓	✗	✓	✗	✓	✓	✓

2008									
B. Abdulhalim et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Anji Wei et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Prajna et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Acharya et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Tabatabaei et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Aileen Sy et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Prajna et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Kosrirukvongs et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
He Wang et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Nejabat et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Kasparova et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓

Kathryn J. Ray et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Vishal Kumar et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Kasetsuwan et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lional Raj Daniel Raj Ponniah et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Y. Matsumoto et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Prajna et al., 2001	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Validad et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kathryn J. Ray et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Qing Li et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Penman et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
O.V. Aleksieieva et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓

P. Garg et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Vimalin Jeyalatha Mani et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Hoffman et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Venkatesh N. Prajna et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yongjing Ji et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kathryn J. Ray et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sarah E Elmohamedy et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Asmaa Reda Metaoe et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Craig W. See et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Prajna et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Bo Zeng et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓

Binh L. Cao et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Penman et al., 2020a	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Hristova et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Eman A. Awad et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mohammed Tawfeek et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ester Sekhose et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Basiony et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Abeer Abdel-Fattah Ali et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Arya et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tong Zhang et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Julie Cho et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review encompasses 80 sources examining treatment options for corneal ulcers, including primary randomized controlled trials, systematic reviews, meta-analyses, and comparative studies. The included studies span bacterial, fungal, viral, and mixed-etiology keratitis, with interventions ranging from topical antimicrobials to surgical adjuncts.

Study	Ulcer Etiology	Sample Size	Key Interventions
M. Srinivasan et al., 2012	Bacterial	500 patients	Prednisolone vs placebo with moxifloxacin
N. Sharma et al., 2013	Bacterial	224 patients	Moxifloxacin vs cefazolin/tobramycin
Vinit M. Shah et al., 2010	Bacterial	61 patients	Fourth-generation fluoroquinolones vs fortified antibiotics
S. Khokhar et al., 2005	Neurotrophic	30 eyes	AMT vs tarsorrhaphy/BCL
D. Ting et al., 2021	Mixed infectious	861 eyes	AMT as adjuvant to SAT
Anna Song et al., 2025	Bacterial	2692 participants	Multiple topical antibiotics
J. Blair et al., 2011	Bacterial	30 eyes	Gatifloxacin ± dexamethasone
A. Dehghani et	Bacterial	89 eyes	Cefazolin-gentamicin vs vancomycin-

Study	Ulcer Etiology	Sample Size	Key Interventions
al., 2009			ceftazidime
N. Sharma et al., 2016	Bacterial	204 patients	Gatifloxacin vs fortified antibiotics
M. Srinivasan et al., 2014	Bacterial	500 patients	Prednisolone vs placebo (12-month outcomes)
Jinghua Liu et al., 2019	Mixed	390 eyes	Cryopreserved AMT
M. Constantinou et al., 2007	Bacterial	229 patients	Moxifloxacin vs ofloxacin vs fortified antibiotics
Sheng Qiu et al., 2015	Fungal	804 participants	Natamycin vs other antifungals
S. Parchand et al., 2012	Fungal	45 eyes	Voriconazole vs natamycin combinations
V. Prajna et al., 2017	Fungal	240 patients	Oral voriconazole vs placebo
J. Katz et al., 2004	Mixed	358 patients	Standard antibiotics ± povidone-iodine
Savitri Sharma et al., 2015	Fungal	118 patients	Voriconazole vs natamycin
Wipawee Booranapong et al., 2004	Bacterial	41 eyes	Lomefloxacin vs ciprofloxacin
Prajna Nv et al.,	Fungal/Acant	330 patients	Rose bengal PDT

Study	Ulcer Etiology	Sample Size	Key Interventions
2025	hamoeba		
Anas E Ahmed et al., 2025	Mixed	322 eyes	AMT effectiveness
T. Thevi et al., 2024	Mixed infectious	Not specified	AMG for persistent epithelial defects
Samim Azizi et al., 2023	Sterile (VKC)	398 patients	Corticosteroid injection vs debridement ± AMT
Ryan Jorge Amorim et al., 2024	Neurotrophic	Not specified	Insulin eye drops
K. Kam et al., 2017	Bacterial/Parasitic	173 eyes	Treatment for orthokeratology-related keratitis
E. McDonald et al., 2014	Bacterial	1823 participants	Fluoroquinolones vs aminoglycoside-cephalosporin
D. Balderson et al., 2015	Viral (herpetic)	432 subjects	Acyclovir vs idoxuridine
A.Z.A.M. AlShammari et al., 2025	Mixed	Not specified	BCLs vs AMT
D. Ting et al., 2019	Mixed infectious	435 patients	PACK-CXL as adjuvant
A. Abbouda et al., 2018	Mixed infectious	145 eyes	PACK-CXL protocols

Study	Ulcer Etiology	Sample Size	Key Interventions
E. McDonald et al., 2014a	Fungal	793 participants	Topical antifungals comparison
M. Srinivasan et al., 2012a	Bacterial	500 patients	SCUT trial design
D. Ting et al., 2020	Mixed infectious	Not specified	AMT systematic review protocol
S. Bamdad et al., 2015	Bacterial	32 patients	CXL for bacterial ulcers
W. Alsarhani et al., 2025	Mixed infectious	Not specified	Povidone-iodine
Naveen Radhakrishnan et al., 2021	Bacterial	279 planned	Steroids and CXL (SCUT II)
M. Srinivasan et al., 2008	Bacterial	42 patients	Pilot corticosteroid trial
B. Abdulhalim et al., 2014	Mixed infectious	40 eyes	Conjunctival flap vs AMG
Anji Wei et al., 2019	Fungal	41 patients	CXL adjuvant for fungal keratitis
N. Prajna et al., 2003	Fungal	116 patients	Econazole vs natamycin
N. Acharya et al., 2009	Bacterial	42 patients	Steroid controversy discussion

Study	Ulcer Etiology	Sample Size	Key Interventions
S. Tabatabaei et al., 2017	Bacterial	99 eyes	Early AMT plus antibiotics
Aileen Sy et al., 2012	Bacterial (Pseudomonas)	500 patients	Corticosteroid effects in Pseudomonas
N. Prajna et al., 2025	Bacterial	280 participants	SCUT II results
P. Kosrirukvongs et al., 2000	Bacterial	41 patients	Ciprofloxacin vs fortified antibiotics
He Wang et al., 2023	Fungal	96 eyes	Hypochlorous acid adjuvant
M. Nejabat et al., 2020	Bacterial	50 patients	Honey vs ciprofloxacin
E. Kasparova et al., 2019	Mixed	37 eyes	Modified CXL
Kathryn J. Ray et al., 2017	Fungal	299 patients	Repeat culture utility
Vishal Kumar et al., 2023	Fungal	Not specified	Liposomal amphotericin B
N. Kasetsuwan et al., 2011	Bacterial	71 eyes	Levofloxacin vs fortified antibiotics
Lional Raj Daniel Raj	Bacterial	35 cases	Drug-depository contact lens

Study	Ulcer Etiology	Sample Size	Key Interventions
Ponniah et al., 2022			
Y. Matsumoto et al., 2010	Fungal (Candida)	29 eyes	Micafungin vs fluconazole
N. Prajna et al., 2001	Bacterial	217 patients	Ofloxacin vs ciprofloxacin
M. Validad et al., 2025	Mixed refractory	30 patients	Povidone-iodine vs CXL
Kathryn J. Ray et al., 2014	Bacterial	500 patients	Early corticosteroid timing
Qing Li et al., 2014	Fungal	210 eyes	Debridement with AMT
A. Penman et al., 2020	Bacterial	Not specified	SCUT summary
O.V. Aleksieieva et al., 2025	Bacterial	98 eyes	HBO therapy plus liposomal ozone
P. Garg et al., 2013	Bacterial (Nocardia)	55 patients	Corticosteroids in Nocardia
Vimalin Jeyalatha Mani et al., 2020	Fungal	20 patients	CXL adjuvant for fungal keratitis
J. Hoffman et al., 2020	Fungal	500 planned	Chlorhexidine vs natamycin

Study	Ulcer Etiology	Sample Size	Key Interventions
Venkatesh N. Prajna et al., 2024	Bacterial	280 patients	SCUT II baseline
Yongjing Ji et al., 2019	Fungal	96 patients	Amphotericin B with autologous serum
Kathryn J. Ray et al., 2018	Fungal	208 corneas	Repeat culture significance
Sarah E Elmohamedy et al., 2023	Fungal	40 eyes	Debridement with intrastromal voriconazole
Asmaa Reda Metaoe et al., 2023	Mixed infectious	40 eyes	Single vs double layer AMT
Craig W. See et al., 2012	Bacterial	500 patients	Prior elicitation for SCUT
N. Prajna et al., 2020	Bacterial	Not specified	CXL for bacterial keratitis (CLAIR)
Bo Zeng et al., 2014	Fungal	20 patients	AMC after debridement
Binh L. Cao et al., 2022	Fungal (Pythium)	306 eyes	Linezolid and azithromycin
A. Penman et al., 2020a	Fungal	Not specified	MUTT summary

Study	Ulcer Etiology	Sample Size	Key Interventions
R. Hristova et al., 2024	Mixed persistent	40 eyes	Autologous serum after AMT
Eman A. Awad et al., 2021	Fungal	40 patients	Topical vs intracameral amphotericin B
Mohammed Tawfeek et al., 2019	Mixed infectious	78 eyes	PACK-CXL adjuvant
Ester Sekhose et al., 2022	Mixed infectious	40 patients	CXL with antimicrobials
A. Basiony et al., 2023	Dormant	50 eyes	PRP eye drops
Abeer Abdel-Fattah Ali et al., 2025	Microbial	40 eyes	Ozone-based eye drops
S. Arya et al., 2008	Mixed infectious	40 patients	AMT adjuvant
Tong Zhang et al., 2020	Mixed	200 patients	Cyclosporine A with glucocorticoid
Julie Cho et al., 2018	Fungal	95 participants	Oral voriconazole (MUTT II)

The studies originated from diverse geographic regions including India, the United States, Australia, Iran, China, Thailand, Nepal, Egypt, and several other countries. The majority of bacterial keratitis trials were conducted in India where agricultural-related trauma

represents the predominant risk factor , while contact lens use was more common in technologically advanced settings .

Antimicrobial Therapy for Bacterial Keratitis

Fluoroquinolones versus Fortified Antibiotics

Multiple randomized controlled trials have compared fluoroquinolone monotherapy against fortified antibiotic combinations for bacterial keratitis management.

Comparison	Healing Rate/Time	Statistical Significance	Authors' Conclusions
Moxifloxacin vs cefazolin/tobramycin	81.8% vs 81.4% at 3 months	P = 0.065 for epithelialization	Equivalent efficacy
Gatifloxacin vs cefazolin/tobramycin	No significant difference	90% CI: -4.5 to 15.3	Equivalent within $\pm 20\%$
Fourth-gen fluoroquinolones vs fortified	93% overall healing	P = 0.98	No difference in efficacy
Moxifloxacin vs ofloxacin vs fortified	94% resolution	P = 0.25 for cure time	No difference between groups
Levofloxacin vs cefazolin/amikacin	96.8% healed	P = 0.81 for resolution	Comparable efficacy
Ofloxacin vs ciprofloxacin	85% vs 77%	P = 0.32	Both effective and safe
Ciprofloxacin vs fortified	70.6% vs 62.5%	Not significant	Alternative to standard therapy

Comparison	Healing Rate/Time	Statistical Significance	Authors' Conclusions
Lomefloxacin vs ciprofloxacin	100% vs 100%	$P > 0.05$	Clinically equivalent

A comprehensive network meta-analysis ranking treatments by healing time identified vancomycin plus ceftazidime (SUCRA 83.8), moxifloxacin (SUCRA 83.1), and cefazolin plus tobramycin (SUCRA 71.3) as the most effective regimens . Compared to ciprofloxacin monotherapy, moxifloxacin demonstrated faster healing by 6.81 days (95% CI -13.83 to 0.20) , while vancomycin plus ceftazidime showed 6.18 days faster healing (95% CI -10.24 to -2.12) .

The systematic review by McDonald et al. found no evidence of difference in comparative effectiveness between fluoroquinolones and aminoglycoside-cephalosporin combinations for treatment success, time to cure, or serious complications . However, safety profiles differed significantly: fluoroquinolones reduced the risk of ocular discomfort and chemical conjunctivitis but increased the risk of white corneal precipitate formation . Fortified tobramycin-cefazolin was approximately three times more likely to cause ocular discomfort than other topical antibiotics .

One RCT comparing cefazolin-gentamicin versus vancomycin-ceftazidime found significantly superior outcomes with the latter regimen: time to stromal infiltration resolution was 17.7 ± 4.3 versus 13.8 ± 3.6 days ($P=0.04$), time to re-epithelialization was 13.2 ± 3.1 versus 9.6 ± 2.7 days ($P=0.01$), and time to anterior chamber clearance was 11.6 ± 2.9 versus 8.1 ± 2.3 days ($P=0.04$) . Ocular burning occurred in 73.1% of patients receiving cefazolin-gentamicin compared to 62.9% with vancomycin-ceftazidime ($P=0.007$).

Adjunctive Corticosteroid Therapy

The role of adjunctive corticosteroids in bacterial keratitis has been extensively evaluated through the Steroids for Corneal Ulcers Trial (SCUT) and related analyses.

Study	Population	Primary Outcome	Key Finding
SCUT (Srinivasan 2012)	500 patients	3-month BSCVA	No overall difference (P = 0.82)
SCUT 12-month (Srinivasan 2014)	399 patients	12-month BSCVA	1-line improvement in non-Nocardia (P = 0.02)
Early timing analysis (Ray 2014)	500 patients	3-month BSCVA	1-line better with early steroids (P = 0.01)
Pseudomonas subanalysis (Sy 2012)	110 P. aeruginosa	3-month BSCVA	No significant benefit or harm
Nocardia subanalysis (Garg 2013)	55 patients	3-month scar size	Larger scars with steroids (0.40 mm, P = 0.02)
Blair 2011	30 eyes	10-week ulcer size	No primary benefit; possible secondary benefit
Pilot trial (Srinivasan 2008)	42 patients	3-month BSCVA	Delayed re-epithelialization (HR 0.47)

Study	Population	Primary Outcome	Key Finding
SCUT II (Prajna 2025)	280 participants	6-month BSCVA	No difference (P = 0.58)

The SCUT trial found no significant overall difference in 3-month best spectacle-corrected visual acuity between prednisolone and placebo groups (-0.009 logMAR; 95% CI, -0.085 to 0.068; P = 0.82). However, significant benefits emerged in specific subgroups: patients with baseline vision of counting fingers or worse showed 0.17 logMAR improvement with corticosteroids (95% CI, -0.31 to -0.02; P = 0.03), and those with ulcers completely covering the central 4-mm pupil showed 0.20 logMAR improvement (95% CI, -0.37 to -0.04; P = 0.02).

Timing of corticosteroid initiation appears critical. When administered within 2-3 days of antibiotic therapy, patients achieved approximately 1-line better visual acuity at 3 months compared to placebo (-0.11 logMAR; 95% CI, -0.20 to -0.02; P = 0.01). Conversely, later administration (≥ 4 days) showed a non-significant trend toward worse outcomes (0.10 logMAR; 95% CI, -0.02 to 0.23; P = 0.14).

At 12-month follow-up, corticosteroid use was associated with a mean 1-line improvement in BSCVA among patients with non-Nocardia ulcers (-0.10 logMAR; 95% CI, -0.19 to -0.02; P = 0.02). In contrast, Nocardia keratitis showed larger scar sizes with corticosteroid treatment (0.47 mm; 95% CI, 0.06-0.88; P = 0.02), suggesting organism-specific responses.

The more recent SCUT II trial found that adjunctive topical difluprednate was not superior to placebo for 6-month visual acuity (-0.04; 95% CI, -0.18 to 0.09; P = 0.58). No significant reduction in corneal perforation or need for therapeutic penetrating keratoplasty was observed.

Antifungal Therapy for Fungal Keratitis

Natamycin versus Voriconazole

Multiple trials have compared natamycin and voriconazole, the two most commonly used topical antifungal agents for filamentous fungal keratitis.

Study	Sample	Healing/Resolution	Visual Outcome	Perforation/TPK
Sharma 2015	118 patients	89.2% vs 66.6% (P = 0.005)	Natamycin superior (P = 0.01)	Not reported
McDonald 2014a (meta-analysis)	793 participants	No difference in failure rates	WMD 0.13 favoring natamycin	RR 1.89 more TPK with voriconazole
Qiu 2015 (meta-analysis)	804 participants	Natamycin superior in Fusarium	-0.18 logMAR favoring natamycin	Lower with natamycin (OR 0.42)
MUTT summary	Not specified	Natamycin superior	Not specified	Not specified

The randomized trial by Sharma et al. demonstrated that significantly more patients treated with natamycin (89.2%) had healed or resolving ulcers compared to voriconazole (66.6%) at final follow-up (P = 0.005). Final visual acuity was significantly better in the natamycin group (P = 0.01). Notably, natamycin showed particular efficacy against Fusarium keratitis (P = 0.005) but not against Aspergillus (P = 0.714).

The meta-analysis by McDonald et al. found that voriconazole was associated with significantly greater risk of requiring therapeutic keratoplasty compared with natamycin (RR

1.89; 95% CI: 1.14, 3.12; number needed to harm = 13) . Final visual acuity was also significantly better with natamycin (WMD 0.13; 95% CI: 0.00, 0.27) .

Other Antifungal Comparisons

Comparison	Findings	Significance
Econazole 2% vs natamycin 5%	No significant difference (P = 0.79)	Econazole as effective as natamycin
Micafungin vs fluconazole (Candida)	No significant difference in healing (41.3 vs 34.4 days)	Comparable efficacy
Oral voriconazole addition	No additional benefit (MUTT II)	Not statistically significant (P = 0.74)
Intracameral amphotericin B	29.6 vs 48.8 days to healing (P < 0.001)	Combined approach superior
Liposomal amphotericin B gel	3.45 ± 1.38 days to improvement	Effective with least vascularization

For Candida keratitis specifically, topical micafungin 0.1% demonstrated comparable efficacy to fluconazole 0.2%, with healing periods of 41.3±38.0 days versus 34.4±37.7 days respectively .

The addition of oral voriconazole to topical antifungal therapy showed no significant benefit. In the MUTT II secondary analysis, patients randomized to oral voriconazole had 1.26-fold increased odds of positive TPK button cultures, though this was not statistically significant (95% CI 0.32-4.87; P = 0.74) . The conclusion was that infection rather than inflammation drives clinical deterioration in many severe fungal ulcers .

Combined topical and intracameral amphotericin B significantly reduced healing time compared to topical amphotericin B alone (29.59 ± 3.24 days versus 48.82 ± 5.31 days; $P < 0.001$).

Viral Keratitis Treatment

For herpetic keratitis, acyclovir 3% ophthalmic ointment demonstrated significant superiority over idoxuridine in a meta-analysis of 432 subjects. At day 7, acyclovir achieved healing in 78% of cases compared to 47% with idoxuridine (OR 3.95; 95% CI: 2.60, 6.00; $P < 0.0001$). This superiority was consistent across ulcer subtypes: dendritic ulcers (OR 4.22; 95% CI: 2.14, 8.32; $P < 0.0001$) and geographic ulcers (OR 5.31; 95% CI: 1.09, 25.93; $P = 0.0244$). Both treatments were generally well tolerated with no serious adverse events reported.

Amniotic Membrane Transplantation

AMT has been evaluated as an adjunctive therapy across multiple infectious keratitis etiologies.

Efficacy Outcomes

Condition	Healing Outcome	Visual Outcome
Bacterial/fungal	4.08 days faster healing ($P < 0.001$)	-0.26 logMAR better UDVA ($P = 0.04$)
Mixed	97% epithelial healing rate	53% vision improvement
Bacterial	Not significantly different	Significantly better BCVA ($P < 0.001$)
Neurotrophic	73.3% vs 66.7% healed ($P > 0.05$)	Both groups improved
Resistant infectious	90% success both groups	No significant difference

Condition	Healing Outcome	Visual Outcome
Mixed	90.9% epithelialization	Improved in central ulcers

The systematic review and meta-analysis by Ting et al. found that adjuvant AMT resulted in shorter mean time to complete corneal healing by approximately 4 days compared to standard antimicrobial treatment alone (−4.08 days; 95% CI −6.27 to −1.88; $P < 0.001$). Better uncorrected visual acuity was observed at 1 month (−0.26 logMAR; 95% CI −0.50 to −0.02; $P = 0.04$). At 6 months, one RCT demonstrated better corrected distance visual acuity and less corneal vascularization (both $P < 0.001$).

Liu et al.'s meta-analysis of 390 eyes reported a pooled corneal epithelium healing rate of 97% ($I^2 = 37.9\%$; 95% CI: 0.94-0.99) and vision improvement rate of 53% ($I^2 = 68.1\%$; 95% CI: 0.42-0.65). Surgical technique influenced outcomes: single-layered inlay, multilayered inlay, and sandwich techniques showed statistically significant differences in both healing and visual improvement rates.

For resistant infectious keratitis, both conjunctival flap and AMG achieved 90% success rates with no significant differences in epithelialization time or visual acuity improvement. However, for large corneal perforations, penetrating keratoplasty may be more appropriate.

Single versus Double Layer AMT

A comparison of single versus double layer AMT for resistant infectious keratitis found no significant difference for mild and moderate corneal ulcers. However, for severe corneal ulcers, double layer AMT achieved successful healing in 83.33% of cases compared to 0% success with single layer AMT. Mean healing time was 5.214 ± 1.888 weeks for single layer versus 4.412 ± 0.712 weeks for double layer.

Corneal Cross-Linking

PACK-CXL for Infectious Keratitis

Photoactivated chromophore for keratitis-corneal cross-linking (PACK-CXL) has been investigated as an adjuvant treatment.

Study	Population	Healing Time	Complications	Conclusions
Ting 2019 (meta-analysis)	435 patients	7.44 days faster (P < 0.0001)	No significant difference	Expedites healing (low-quality evidence)
Tawfeek 2019	78 eyes	7.02 vs 10.87 weeks (P = 0.002)	Lower failure rate (2.6% vs 23.1%)	Synergistic effect
Bamdad 2015	32 patients	17.2 vs 24.7 days	Reduced need for surgery	Beneficial for moderate bacterial
Abbouda 2018 (review)	145 eyes	25.7±29.8 days	84.1% blocked corneal melting	Needs protocol optimization
Kasparova 2019	37 eyes	29.6 vs 50.4 days (P < 0.05)	75% complete reduction	42% reduced treatment duration

The meta-analysis by Ting et al. found adjuvant PACK-CXL resulted in 7.44 days shorter mean time to complete corneal healing (95% CI, -10.71 to -4.16) and quicker resolution of infiltrate at 7 days (-5.49 mm²; 95% CI, -7.44 to -3.54). Success rates varied by etiology: bacterial (84.8%), fungal (73.5%), Acanthamoeba (66.7%), and culture-negative (92.0%).

However, PACK-CXL efficacy depends on ulcer depth and width. In infiltrations affecting the entire stromal thickness, efficacy decreased to 66.6%, and in cases extending to Descemet's membrane with area >7 mm, clinical effect was absent or insufficient .

CXL for Bacterial Keratitis

Study	Outcome	Finding
CLAIR trial (Prajna 2020)	24-hour culture positivity	0.60 decreased odds (95% CI: 0.10-3.50; P = 0.65)
SCUT II (Prajna 2025)	6-month scar size	Increased with CXL (0.56 mm; P = 0.02)
Sekhose 2022	Healing time	Slower healing (44.5 vs 27.7 days; P = 0.00)

The CLAIR trial was unable to confirm a benefit to adjuvant CXL in the primary treatment of moderate bacterial keratitis . Visual acuity was 0.9 logMAR lines worse and scar size 0.41 mm larger in the CXL group at 3 months, though neither reached statistical significance . However, fewer corneal perforations or need for therapeutic penetrating keratoplasty were noted in the CXL group .

Paradoxically, the SCUT II trial found that CXL plus corticosteroids increased scar size compared to steroids alone (0.56 mm; 95% CI, 0.20-0.92; P = 0.02) , suggesting that this combined approach may not be superior to topical antibiotics alone .

CXL for Fungal Keratitis

Study	Outcome	Effect
Wei 2019	Ulcer healing	Significantly faster (P < 0.05)
Mani 2020	Resolution time	Significantly shorter

For fungal keratitis, adjuvant CXL accelerated healing, shortened treatment duration, and minimized the need for medications and surgery . The study by Mani et al. demonstrated significant downregulation of inflammatory markers (IL-1 β , IL-8, IFN- γ) and toll-like receptors (TLR-3, TLR-4, TLR-6) following CXL .

Novel and Adjunctive Therapies

Antiseptic Agents

Agent	Comparison	Findings	Quality
Povidone-iodine 2.5%	Added to antibiotics	No improved visual outcomes (RR 1.77; 95% CI 0.62-5.03)	Limited
Povidone-iodine 1% vs CXL	Refractory ulcers	Both 60-73% improvement; no significant difference	Low
Chlorhexidine 0.2%	Vs natamycin (ongoing)	Non-inferiority threshold: 0.15 logMAR	Protocol only

The systematic review by Alsarhani et al. found mixed evidence for povidone-iodine: one study showed effectiveness in reducing infiltrate and ulcer size while awaiting cultures, while others found no significant benefit when added to standard antibiotic treatment . No safety concerns were reported with topical povidone-iodine .

Novel Topical Agents

Agent	Condition	Outcome	Statistical Significance
Honey 70%	Foreign body-induced	3.88 vs 6.32 days	Faster epithelial

Agent	Condition	Outcome	Statistical Significance
		healing (P = 0.020)	healing
Hypochlorous acid 0.01%	Fungal keratitis	Faster healing (P < 0.01)	Grade I and II ulcers
Ozone-based drops	Microbial keratitis	83.4% vs 70.5% ulcer reduction (P = 0.029)	Promotes faster healing
PRP eye drops	Dormant ulcers	88% vs 48% clinical improvement (P = 0.004)	Superior healing outcomes
Autologous serum	Post-AMT	0.14 vs 0.08 VA improvement (P = 0.00046)	Better visual acuity

Honey-based ophthalmic formulation (70%) demonstrated significantly faster corneal epithelial defect healing compared to ciprofloxacin (3.88±3.44 vs 6.32±3.69 days; P = 0.020), though no significant difference was observed for corneal infiltration healing.

Hypochlorous acid (0.01%) combined with conventional treatment accelerated healing of fungal keratitis without obvious complications. For grade I patients, all cases achieved cure with faster healing speed, while grade II patients showed significantly faster recovery time and hypopyon disappearance.

Platelet-rich plasma eye drops showed clinical improvement in 88% of eyes with dormant corneal ulcers, with 72% achieving complete response compared to only 28% complete response in the conventional therapy group (P = 0.004).

Drug Delivery Innovations

A novel drug-depository contact lens (DDCL) for bacterial keratitis demonstrated significantly faster recovery compared to topical treatment alone . Complete recovery occurred at day 5 in the DDCL group versus day 14 in the topical-only group . The DDCL may eliminate the necessity for loading doses by prolonging corneal antimicrobial availability .

Hyperbaric Oxygen and Ozone Therapy

HBO therapy plus liposomal ozone-based solution significantly reduced treatment duration for bacterial keratitis . Time to resolution of infiltration was reduced by 5.9 ± 0.2 days compared to control, corneal re-epithelialization completed 8.2 ± 0.2 days earlier, and hospital stay decreased by 6.6 ± 0.2 days (all $P < 0.001$) .

Surgical Adjuncts

Debridement with Adjunctive Therapy

For fungal keratitis, corneal debridement combined with AMT coverage achieved 91.09% efficacy compared to 75.23% with debridement alone ($P < 0.05$) . The mean therapeutic course was significantly shorter (22.4 ± 1.8 vs 33.2 ± 2.4 days; $P < 0.05$) .

Corneal debridement combined with intrastromal voriconazole injection achieved healing in 95% of recalcitrant fungal keratitis cases at 4 weeks compared to 55% with topical therapy alone ($P = 0.002$) .

Amphotericin B with Autologous Serum

Injection therapy combining amphotericin B with autologous serum achieved 93.75% total effective rate compared to 75.00% with amphotericin B alone ($P = 0.011$) .

Improvement times for hypopyon, corneal ulcer, foreign body sensation, and photophobia were all significantly shorter in the combination group (all $P < 0.001$).

Prognostic Factors and Treatment Predictors

Baseline Characteristics Predicting Outcomes

Factor	Effect on Outcome	Evidence
Baseline visual acuity	Strong predictor of final VA	SCUT and multiple trials
Infiltrate size	Larger infiltrates = worse outcomes	OR 1.37 per 1-mm increase
Hypopyon presence	2.28x odds of perforation/TPK	MUTT II analysis
Infiltrate depth	Posterior third involvement = 71.4% perforation/TPK risk	MUTT II analysis
Ulcer location	Central ulcers benefit more from corticosteroids	SCUT
Duration of symptoms	Longer duration = worse prognosis	Nocardia analysis

For fungal keratitis specifically, age ≥ 45 years (95% CI, 1.15-60; $P = 0.036$) and epithelial defect area ≥ 36 mm² (95% CI, 2.56-151.49; $P = 0.004$) were identified as the most significant risk factors for primary treatment failure.

Microbiological Predictors

Repeat culture positivity at day 6 strongly predicted poor outcomes in fungal keratitis. Patients with positive cultures had 6.27-fold increased odds of corneal perforation or need for TPK (95% CI: 2.73-14.40; $P < 0.001$), 0.39 logMAR worse visual acuity ($P < 0.001$), and slower re-epithelialization (HR 0.33; 95% CI: 0.21-0.50; $P < 0.001$).

For *Pythium* keratitis, high rates of TPK (80%; 95% CI 70-87%) and globe removal (25%; 95% CI 13-43%) were observed. Use of azithromycin was associated with lower TPK rates (RR = 0.80; 95% CI 0.67-0.96).

Complications and Safety Profiles

Corneal Perforation Rates

Study Population	Perforation Rate	Associated Factors
SCUT (bacterial)	No significant difference between arms	Ulcer severity
MUTT II (fungal)	50.8% perforation/TPK	Hypopyon, infiltrate size/depth
Orthokeratology-related	10% needed surgical treatment	Delayed diagnosis
<i>Pythium</i> keratitis	80% required TPK	Organism virulence

Treatment-Specific Adverse Effects

Fluoroquinolones demonstrated better ocular tolerability than fortified antibiotics. Chemical conjunctivitis and ocular discomfort were less frequent with fluoroquinolones, though white corneal precipitates occurred more commonly with ciprofloxacin (11.1%).

For PACK-CXL, there was no significant difference in risk of adverse events compared to standard antimicrobial treatment alone (RR 0.84; 95% CI 0.26 to 2.71) . Potential risks include endothelial dysfunction in corneas with thickness <400 μ m and possible exacerbation of herpes simplex infection .

Corticosteroid use was associated with potential for delayed re-epithelialization (HR 0.47; 95% CI 0.23 to 0.94) and larger scar formation specifically in Nocardia keratitis . No increased perforation risk was observed in the SCUT trial .

Synthesis

The evidence synthesis reveals several key patterns that help reconcile apparently conflicting findings across studies.

Antimicrobial Selection

For bacterial keratitis, fluoroquinolone monotherapy demonstrates equivalent efficacy to fortified antibiotic combinations across multiple well-powered trials . The choice between these regimens should therefore be guided by practical considerations: fluoroquinolones offer convenience (commercial availability, no refrigeration requirement, less frequent dosing), better tolerability (lower rates of ocular discomfort and chemical conjunctivitis) , while fortified combinations may provide broader coverage for polymicrobial infections or suspected resistant organisms. The network meta-analysis suggesting vancomycin-ceftazidime superiority should be interpreted cautiously given the low-quality evidence base.

For fungal keratitis, natamycin consistently outperforms voriconazole for filamentous fungi, particularly *Fusarium* species . This organism-specific effect explains some heterogeneity in earlier studies—trials with higher *Aspergillus* proportions show less pronounced differences between agents . Voriconazole remains valuable for *Candida* keratitis and potentially for *Aspergillus*, where its broader spectrum and better penetration may offer advantages.

Adjunctive Corticosteroid Use

The apparent conflict between the negative overall SCUT result and positive subgroup findings can be reconciled by recognizing distinct patient populations:

1. **Early intervention (≤ 3 days)** : Patients receiving corticosteroids within 2-3 days of antibiotic initiation showed significant benefit (1-line improvement)
2. **Severe presentation** : Patients with counting fingers or worse baseline vision benefited significantly
3. **Central ulcers** : Those with ulcers covering the central 4-mm pupil showed improvement
4. **Non-Nocardia organisms** : Long-term (12-month) outcomes improved with corticosteroids only in non-Nocardia cases

Conversely, corticosteroids appear contraindicated for Nocardia keratitis, where they produce larger scars without visual benefit . The critical determinant appears to be timing and organism identification—clinicians should consider early addition of corticosteroids in severe, centrally-located bacterial ulcers while awaiting culture results, but discontinue if Nocardia is identified.

Surgical Adjuncts

AMT demonstrates consistent benefit across etiologies, reducing healing time by approximately 4 days and improving visual outcomes . The effect size appears modest for mild-moderate ulcers but substantial for severe or refractory cases. Single-layer AMT suffices for most cases, but severe corneal ulcers specifically benefit from double-layer technique .

PACK-CXL shows promise for infectious keratitis with faster healing times , but the recent SCUT II results showing increased scar size with combined CXL and steroids

suggest the optimal role remains undefined. PACK-CXL may be most valuable for resistant cases or where reducing microbial burden is prioritized over minimizing scarring.

Methodological Considerations Affecting Interpretation

Several factors limit definitive conclusions:

1. **Geographic bias** : Most large trials were conducted in India where agricultural trauma predominates . Pathogen distributions and antibiotic resistance patterns may differ in other settings.
2. **Severity spectrum** : Studies enrolling severe ulcers (MUTT, SCUT) may not apply to milder presentations seen in primary care settings.
3. **Outcome heterogeneity** : Endpoints varied from healing time to visual acuity to microbiological cure, complicating cross-study comparisons.
4. **Evidence quality** : Network meta-analyses rated most comparisons as low or very low certainty , and systematic reviews consistently noted high risk of bias in included trials .

The evidence supports a treatment algorithm stratified by etiology, severity, and timing: initial broad-spectrum coverage (fluoroquinolone for mild-moderate bacterial, fortified antibiotics for severe or polymicrobial suspected, natamycin for filamentous fungal), followed by targeted adjustment based on culture results and clinical response. Adjunctive interventions (early corticosteroids for severe non-Nocardia bacterial keratitis, AMT for non-healing or severe ulcers, CXL for selected refractory cases) should be considered based on individual patient factors rather than applied universally.

DISCUSSION

This systematic review synthesizes evidence from 80 studies to provide a comprehensive overview of the management strategies for corneal ulcers. The discussion will interpret the findings, reconcile conflicting data, explore clinical implications, and address limitations.

Reconciling Evidence on Antimicrobial Therapy

For bacterial keratitis, the accumulated evidence robustly supports the equivalence of modern fluoroquinolone monotherapy (e.g., moxifloxacin, gatifloxacin) to traditional fortified antibiotic combinations (e.g., cefazolin/tobramycin) in terms of healing rates and time to cure (Sharma et al., 2013; Constantinou et al., 2007). However, the choice between these regimens extends beyond mere efficacy. Fluoroquinolones offer significant practical advantages, including commercial availability, simpler dosing schedules, and no requirement for refrigeration or compounding, which reduces preparation errors and improves patient adherence (McDonald et al., 2014). Importantly, they demonstrate a superior tolerability profile, with significantly lower rates of ocular discomfort and chemical conjunctivitis compared to fortified tobramycin-cefazolin (McDonald et al., 2014). Nevertheless, the network meta-analysis by Song et al. (2025) suggesting the superiority of vancomycin-ceftazidime, supported by a smaller RCT showing faster resolution of signs (Dehghani et al., 2009), indicates that fortified regimens may retain a crucial role. This role is likely in settings with high rates of resistant organisms (e.g., methicillin-resistant *Staphylococcus aureus*), polymicrobial infections, or in severe ulcers where broader empirical coverage is deemed essential before culture results are available. Therefore, the decision is not one of superiority but of context-driven selection.

The fungal keratitis data present a clearer hierarchy. Natamycin 5% consistently emerges as the superior first-line agent for filamentous fungi, particularly *Fusarium* species, demonstrating higher healing rates, better final visual acuity, and a lower risk of progressing to therapeutic penetrating keratoplasty (TPK) compared to voriconazole 1% (Sharma et al., 2015; McDonald et al., 2014a). This organism-specific efficacy is a key finding that resolves earlier heterogeneous trial

results; studies with a higher proportion of *Aspergillus* ulcers show less pronounced differences (Parchand et al., 2012). Voriconazole, with its broader spectrum and better intraocular penetration, remains valuable for *Candida* keratitis and as a second-line or systemic agent for deep infections. The lack of benefit from adding oral voriconazole in the MUTT II trial underscores that in severe fungal keratitis, local disease control is paramount, and systemic therapy may not augment outcomes (Cho et al., 2018).

The Nuanced Role of Adjunctive Corticosteroids

The data on corticosteroids illustrate the complexity of corneal ulcer management, where a one-size-fits-all approach is ineffective. The overall null result of the SCUT trial masked significant benefits in specific, high-risk subgroups (Srinivasan et al., 2012). This review identifies a clear profile for potential steroid benefit: patients with severe bacterial keratitis (baseline vision of counting fingers or worse), centrally located ulcers (covering the central 4-mm pupil), and non-*Nocardia* etiology, particularly when steroids are initiated early (within 2-3 days of effective antibiotic therapy) (Ray et al., 2014; Sy et al., 2012). In these cases, early inflammatory modulation appears to limit stromal destruction and scarring, translating to a 1-line visual acuity improvement. Conversely, corticosteroids are contraindicated in *Nocardia* keratitis, where they are associated with larger scar sizes (Garg & Vazirani, 2013). The more recent SCUT II trial, which failed to show benefit for difluprednate, may reflect differences in the steroid potency, patient population, or the confounding effect of combined CXL (Prajna et al., 2025). The critical clinical takeaway is the necessity for a stratified approach: consider early adjunctive corticosteroids in severe, central, bacterial ulcers while awaiting culture, but have a low threshold to discontinue if *Nocardia* or clinical worsening occurs.

Surgical and Procedural Adjuncts: Defining Their Place

Amniotic Membrane Transplantation (AMT) has solidified its role as a valuable adjunct. The meta-analysis by Ting et al. (2021) confirms it reduces healing time by approximately 4 days and improves uncorrected visual acuity, primarily through its anti-inflammatory, anti-fibrotic, and

pro-healing biological properties. Its utility spans infectious, neurotrophic, and persistent epithelial defects (Khokhar et al., 2005; Thevi et al., 2024). The technique matters: for severe ulcers, a double-layer AMT provides significantly better success rates than a single layer, likely due to improved mechanical support and sustained biological factor release (Metaoe et al., 2023).

Photoactivated chromophore for keratitis-corneal cross-linking (PACK-CXL) presents a more complex picture. While meta-analyses indicate it can expedite healing and infiltrate resolution (Ting et al., 2019), its efficacy is highly dependent on ulcer parameters. It shows reduced effectiveness in very deep ulcers or those with extensive area, and crucially, the SCUT II trial found that CXL combined with steroids resulted in *larger* scars than steroids alone (Prajna et al., 2025; Abbouda et al., 2018). This suggests that while the antimicrobial photochemical effect of CXL may be beneficial, the cross-linking of collagen in an actively inflamed, infected cornea might impede normal remodeling and lead to more opaque scarring. Therefore, PACK-CXL might be best reserved for select cases of progressive, resistant microbial keratitis where reducing microbial burden is the immediate priority, rather than as a routine adjuvant.

Novel Therapies and Future Directions

The review highlights several promising novel therapies. Honey-based formulations and hypochlorous acid demonstrated faster epithelial healing in specific contexts (Nejabat et al., 2020; Wang et al., 2023). Platelet-rich plasma (PRP) and autologous serum eye drops show significant promise in treating dormant ulcers and enhancing healing post-AMT, likely due to high concentrations of growth factors (Basiony et al., 2023; Hristova et al., 2024). Innovations in drug delivery, such as drug-depository contact lenses, could revolutionize treatment by ensuring sustained drug delivery, improving compliance, and potentially improving outcomes (Ponniah et al., 2022).

Prognostic Factors and Personalized Medicine

Identifying predictors of outcome is a step towards personalized medicine. Factors like large infiltrate size, presence of hypopyon, deep stromal involvement, and positive repeat culture at day 6 (for fungal ulcers) are robust indicators of a high risk for perforation or TPK (Prajna et al., 2017; Ray et al., 2018). These patients should be monitored more closely and considered earlier for aggressive medical or surgical interventions. The devastating prognosis of *Pythium* keratitis, with its high rates of TPK and enucleation, underscores the need for rapid molecular diagnosis and novel therapeutic protocols (Cao et al., 2022).

Limitations and Clinical Implications

The evidence synthesis is constrained by several factors. Geographic bias is prominent, with major trials conducted in South Asia, where trauma and fungal keratitis are prevalent. Findings may not directly translate to Western settings dominated by contact lens-related bacterial keratitis. Outcome heterogeneity across studies complicates direct comparisons. Finally, the quality of evidence for many comparisons, particularly in network meta-analyses, is often rated as low or very low certainty.

Despite these limitations, a clear clinical algorithm emerges. Management must be etiology-driven. Start with appropriate empirical therapy (fluoroquinolone for mild-moderate bacterial; consider fortified for severe; natamycin for fungal). Adjust based on culture and clinical response at 48-72 hours. Add early corticosteroids only for severe, central, non-*Nocardia* bacterial ulcers. Employ AMT for persistent epithelial defects or non-healing ulcers. Consider PACK-CXL or other novel adjuncts (e.g., PRP) for specific, refractory cases within their evidence base. Ultimately, successful management requires not just knowledge of drug efficacy but also astute clinical judgment, careful patient monitoring, and a willingness to escalate therapy based on predefined warning signs.

CONCLUSION AND RECOMMENDATIONS

Conclusion: The management of corneal ulcers is multifaceted, requiring an integrated approach that combines accurate microbiological diagnosis, timely and appropriate antimicrobial therapy, and selective use of adjunctive interventions. Evidence confirms the non-inferiority of fluoroquinolone monotherapy for bacterial keratitis, the superiority of natamycin for filamentous fungal keratitis, and the conditional benefit of early adjunctive corticosteroids in severe, non-*Nocardia* bacterial cases. Surgical adjuncts like AMT are effective in promoting healing, while the role of PACK-CXL is more nuanced and should be applied judiciously. Prognostic factors such as ulcer size, depth, and culture persistence are critical in stratifying patient risk and guiding management intensity.

Recommendations:

1. **Clinical Practice:** Adopt a stratified treatment protocol based on ulcer severity, location, and likely etiology. Implement early follow-up (48-72 hours) to assess response and adjust therapy. Use corticosteroids selectively based on the SCUT subgroup criteria and avoid them in confirmed *Nocardia* cases.
2. **Health Systems:** Support access to essential antimicrobials like natamycin and moxifloxacin. Develop capacity for basic microbiological diagnosis, including staining and culture, which is fundamental to targeted therapy.
3. **Future Research:** Conduct high-quality RCTs in diverse geographic populations to improve generalizability. Standardize core outcome sets for corneal ulcer trials to facilitate meta-analysis. Investigate personalized medicine approaches using biomarkers and host-genetic factors. Prioritize research into novel therapies for resistant pathogens like *Pythium* and effective drug-delivery systems.

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