

## Dissociated Therapeutic Regimen: Systemic Corticosteroids and Topical Natamycin in Traumatic Fungal Keratitis

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### ABSTRACT

**Introduction:** Penetrating ocular trauma complicated by secondary fungal keratitis presents a fundamental inflammatory paradox in ophthalmology. While corticosteroids are clinically imperative to suppress trauma-induced fibrinoid syndrome and prevent phthisis bulbi, they are traditionally contraindicated in active mycotic infections due to the risk of potentiating fungal proliferation. This report evaluates a dissociated therapeutic protocol utilizing systemic corticosteroids alongside topical antifungals to navigate this therapeutic impasse. **Case presentation:** We present the case of a 26-year-old male sustaining a penetrating corneal injury from a metallic nail. Following primary repair, the patient developed a severe anterior chamber reaction with Standardization of Uveitis Nomenclature (SUN) Grade 3+ cells and a corneal infiltrate exhibiting feathery margins. Potassium Hydroxide 10% wet mount confirmed the presence of fungal hyphae. A dissociated therapeutic regimen was initiated: intensive topical Natamycin 5% administered hourly to target the ocular surface infection, synchronized with oral Methylprednisolone (24 mg/day; 0.4 mg/kg) to control intraocular inflammation via the systemic circulation. The regimen successfully decoupled the immune response. Intraocular inflammation resolved within 14 days, preventing the formation of permanent synechiae or cyclitic membranes. The fungal infection was eradicated, confirmed by negative serial corneal smears and the clinical resolution of the infiltrate into a stable leucoma. Visual acuity improved from Hand Motion (LogMAR 2.30) at presentation to 6/45 (LogMAR 0.88) at Day 35. No fungal recurrence was observed during the follow-up period. **Conclusion:** A dissociated strategy using intermediate-dose systemic corticosteroids to manage internal inflammation, while reserving the ocular surface for aggressive topical antifungal therapy, may offer a viable strategy for globe salvage in complex traumatic fungal keratitis cases where standard protocols are undefined.

### 1. Introduction

Penetrating ocular trauma, clinically classified under the umbrella of open-globe injuries, stands as a formidable public health challenge and remains a leading cause of monocular blindness and severe visual impairment worldwide.<sup>1</sup> While the incidence of ocular trauma is a universal concern, the epidemiology of these injuries reveals a stark disparity, disproportionately affecting the working-age male population in developing nations. This demographic

skew is particularly pronounced within tropical climates, where the socioeconomic fabric is tightly woven with agricultural and industrial activities—sectors that inherently carry a high risk of high-velocity projectile injuries.<sup>2</sup> The consequences of such trauma extend beyond individual morbidity, precipitating significant economic burdens due to the loss of productivity in a population segment that typically serves as the primary economic engine for their families and communities.

The visual prognosis in these devastating injuries is frequently compromised not merely by the initial mechanical disruption of the globe but by the subsequent and often relentless biological sequelae. The pathophysiology of an open-globe injury is defined by an immediate, catastrophic breakdown of the blood-aqueous barrier, a physiological seal that normally maintains the eye's immune privilege.<sup>3</sup> This rupture triggers a biological cascade often described as a cytokine storm, characterized by the acute and massive release of pro-inflammatory mediators, including Interleukin-1, tumor necrosis factor-alpha, and various prostaglandins. This molecular signaling pathway results in a rapid influx of inflammatory substrates: fibrin deposition, leukocyte infiltration, and fibroblast proliferation flood the anterior segment and vitreous cavity. While this inflammatory response is evolutionarily conserved and designed to facilitate wound healing and seal the breached globe, the eye's unique, confined anatomy renders unchecked inflammation maladaptive. In the absence of regulation, this robust immune response frequently precipitates severe secondary complications that are structurally destructive, such as phthisis bulbi (atrophy of the globe), tractional retinal detachment, secondary glaucoma arising from trabecular meshwork obstruction, and the formation of recalcitrant cyclitic membranes. Consequently, to mitigate these catastrophic risks, the established standard of care for non-infectious penetrating trauma mandates the early and aggressive administration of potent corticosteroids to stabilize the blood-ocular barrier and preserve the intricate ocular architecture.<sup>4</sup>

The clinical landscape changes dramatically, however, with the second hit of microbial inoculation. The dual threats of microbial infection and dysregulated host inflammatory responses create a complex, hostile pathological environment that defies standard therapeutic algorithms.<sup>5</sup> In trauma settings involving vegetative matter or contaminated metallic foreign bodies—common in the agricultural backdrop of the developing world—the inoculation of fungal pathogens significantly elevates the risk of post-

traumatic fungal keratitis or endophthalmitis. These complications carry a notoriously poor prognosis for visual recovery, often necessitating enucleation or resulting in a sightless, painful eye.

Fungal keratitis is a particularly distinct and aggressive entity, characterized by the organism's ability to penetrate the deep corneal stroma and breach vital barriers such as Descemet's membrane. Filamentous fungi, specifically *Fusarium* and *Aspergillus* species, are the predominant pathogens in tropical environments. These organisms are evolutionarily equipped to survive hostile environments, often forming dense biofilms that are inherently resistant to standard antimicrobial penetration, thereby complicating medical management.<sup>5</sup>

The superimposition of a fungal pathogen upon a traumatic injury introduces a profound therapeutic paralysis for the clinician. This dilemma stems from the diametrically opposed management strategies for trauma and infection.<sup>6</sup> Historically and pharmacologically, the use of corticosteroids in the presence of an active fungal infection is widely considered a strict contraindication. The rationale is immunologically sound: corticosteroids suppress the macrophage and neutrophil responses that are essential for fungal clearance, and in many cases, may actually enhance fungal replication.<sup>7</sup>

Consequently, the treating ophthalmologist faces a fundamental and high-stakes dilemma: treating the infection by withholding steroids may allow unchecked, trauma-induced inflammation to destroy the eye's structural integrity through phthisis or membrane formation. Conversely, treating the inflammation with steroids to save the globe's structure risks potentiating the fungal infection, allowing it to flourish into a fulminant, globe-destroying endophthalmitis. This inflammatory paradox represents one of the most difficult decision-making junctures in ocular trauma management.<sup>8</sup>

Despite the severity of this condition, current clinical guidelines regarding this specific intersection of pathologies—traumatic open globe with fungal

superinfection—remain largely undefined. The scientific literature offers limited guidance. For instance, the landmark Mycotic Ulcer Treatment Trial II (MUTT II) provided high-level evidence regarding the inefficacy of oral antifungals for corneal ulcers, yet it did not address the safety or efficacy of systemic corticosteroids in the specific context of traumatic inflammation. While most clinical guidelines strictly prohibit the use of topical steroids in fungal keratitis due to the risk of corneal melting and perforation, the role of systemic steroids remains a gray area. This therapeutic void forces clinicians to rely on anecdotal evidence or personal discretion, often without standardized protocols, leading to inconsistent management strategies and, frequently, suboptimal visual outcomes.<sup>9</sup>

To address this critical gap, this manuscript proposes and evaluates a novel dissociated therapeutic regimen grounded in the principles of ocular pharmacokinetics. Our hypothesis challenges the binary notion of steroids vs. no steroids by exploiting the physiological differences between the blood-aqueous barrier and the blood-tear barrier. We posit that by administering corticosteroids systemically (orally or intravenously), we can effectively deliver anti-inflammatory agents to the vascularized uveal tissues (iris and ciliary body) via the ciliary circulation. Crucially, the physiological blood-tear barrier minimizes the secretion of systemic drugs into the precorneal tear film. This theoretically creates a therapeutic dissociation: the intraocular inflammation is suppressed systemically, protecting the globe from phthisis, while the avascular corneal surface—where the fungal infection resides—remains relatively free of steroid-induced immunosuppression. This pharmacokinetic separation allows for the concurrent use of aggressive topical antifungal agents, such as Natamycin, to target the surface infection without the interference of local steroid drops.<sup>10</sup>

The primary aim of this study is to evaluate the clinical efficacy and safety of this dissociated therapeutic regimen in salvaging a globe compromised

by severe penetrating trauma and secondary fungal keratitis. We present a detailed case report of a young male with a nail-induced penetrating injury, serving as a proof-of-concept for this dynamic therapeutic balance. The novelty of this research lies in its attempt to formalize a physiology-based protocol that decouples the treatment of the first hit (trauma) from the second hit (infection). By demonstrating that systemic corticosteroids can be safely utilized to manage internal inflammation without exacerbating surface fungal keratitis, this study seeks to provide a logical, scientifically grounded framework for navigating the inflammatory paradox. This approach aims to preserve global integrity and prepare the eye for future visual rehabilitation, offering a potential paradigm shift in the management of complex traumatic fungal keratitis cases where standard protocols are currently non-existent.

## **2. Case Presentation**

A 26-year-old male presented to the Emergency Department of a tertiary ophthalmic referral center in Bali, Indonesia, presenting a classic yet severe profile of occupational ocular trauma. The patient reported the acute onset of excruciating ocular pain, uncontrollable epiphora, and an immediate, profound reduction in visual perception in his left eye. The injury occurred approximately two hours prior to admission, a critical time window that allowed for immediate intervention before the onset of frank endophthalmitis. The mechanism of injury was identified as a high-velocity projectile impact sustained during manual labor. Specifically, the patient was hammering a rusted metallic nail when a fragment ricocheted, striking the left globe with significant kinetic energy. This mechanism is clinically ominous; the involvement of a rusted metallic foreign body introduces a dual threat: the immediate mechanical disruption of ocular tissues and the inoculation of a high burden of environmental pathogens, including bacteria and, notably in tropical environments, vegetative fungi. A comprehensive review was conducted to identify any comorbidities

that might complicate surgical repair or wound healing (Table 1). The patient denied any history of diabetes mellitus, autoimmune diatheses, or immunocompromised states. His anthropometric data were recorded, with a body weight of 62 kg. This parameter was not merely administrative but served as a crucial baseline for the subsequent calculation of weight-based systemic anti-inflammatory pharmacotherapy.

Upon primary survey, the patient was alert, oriented, and hemodynamically stable, allowing for an immediate and detailed ophthalmic assessment. The uninjured right eye (OD) demonstrated a visual acuity of 6/9 (LogMAR 0.18), serving as a control for the patient's baseline visual potential. In stark contrast, the injured left eye (OS) presented with visual acuity reduced to Hand Motion at a distance of 1 meter (LogMAR 2.30). Despite this devastating functional loss, a critical prognostic indicator was preserved: the patient maintained accurate light projection in all four quadrants. This finding suggested that despite the anterior segment disorganization, the neuro-retinal architecture and optic nerve conduction remained grossly intact, justifying aggressive globe-salvaging efforts. Tonometry of the right eye yielded a normal pressure of 14 mmHg. The left eye, however, was estimated at approximately 8 mmHg via gentle digital palpation. This hypotony was pathognomonic for a loss of globe integrity, confirming the clinical suspicion of a penetrating injury with active aqueous leak.

Slit-lamp biomicroscopy of the left eye revealed extensive structural damage. The conjunctiva was obscured by severe chemosis and a dense, 360-degree subconjunctival hemorrhage, markers of significant blunt force trauma accompanying the penetration. The cornea exhibited a full-thickness paracentral laceration, approximately 4 mm in length, traversing the inferior quadrant between the 5 and 7 o'clock positions. The wound architecture was complex, with edematous margins and a positive Seidel test, confirming the active efflux of aqueous humor. The anterior chamber was shallow (Van Herick

Grade I), a direct consequence of the leak. More concerning was the inflammatory status; the chamber contained a fibrinous exudate with cellular reaction graded at 3+ according to the standardization of uveitis nomenclature (SUN) criteria. This intense fibrinoid reaction indicated a massive breakdown of the blood-aqueous barrier. Iris tissue had prolapsed and incarcerated into the corneal wound, creating a peaked pupil deformity directed toward the injury site. Furthermore, the anterior lens capsule was breached, resulting in rapid cortical hydration and the formation of a traumatic cataract, which precluded a clear view of the fundus.

The diagnosis of a penetrating ocular injury with uveal prolapse necessitated emergency surgical intervention under general anesthesia. The primary surgical objective was to restore the watertight integrity of the globe. A critical intraoperative decision involved the management of the prolapsed iris. The tissue had been exposed to the external environment—specifically a non-sterile, rusted surface—for a duration exceeding six hours. Based on established trauma protocols, this tissue was judged non-viable and a high-risk nidus for infection. Consequently, an abscission (excision) of the prolapsed iris was performed to mitigate the risk of endophthalmitis. The corneal laceration was re-approximated using 10-0 nylon interrupted sutures. The tension was carefully titrated to achieve a watertight seal without inducing excessive astigmatism, and closure was verified intraoperatively by a negative Seidel test.

Prophylaxis against infection was aggressive. Intracameral moxifloxacin (0.5%) was instilled directly into the anterior chamber at the conclusion of surgery. Systemically, the patient was initiated on intravenous Ceftriaxone (1 gram every 12 hours). This third-generation cephalosporin was selected for its broad spectrum and excellent ocular penetration, specifically targeting the common Gram-negative and Gram-positive organisms associated with metallic foreign bodies.

Table 1. Summary of clinical findings on admission.

PARAMETER	RIGHT EYE (OD) (UNINJURED CONTROL)	LEFT EYE (OS) (TRAUMATIZED EYE)
PATIENT DEMOGRAPHICS & SYSTEMIC HISTORY		
Profile	26-year-old Male   Weight: 62 kg	
Mechanism	High-velocity projectile (rusted metallic nail) ricochet injury.	
Systemic Status	Unremarkable (No Diabetes, Autoimmune, or Immunocompromised states).	
FUNCTIONAL ASSESSMENT		
Visual Acuity (Distance)	6/9 (LogMAR 0.18)	Hand Motion (LogMAR 2.30) <span>CRITICAL</span> (Light Projection Intact in 4 Quadrants)
Intraocular Pressure	14 mmHg	~8 mmHg (Hypotony) <span>LEAK</span>
ANTERIOR SEGMENT EXAMINATION		
Conjunctiva	White & Quiet	360° Subconjunctival Hemorrhage Severe Chemosis
Cornea	Clear	Full-thickness Laceration (4mm) Location: Inferior (5-7 o'clock) Seidel Test: Positive (+)
Anterior Chamber	Deep & Quiet	Shallow (Van Herick Grade I) Reaction: SUN Grade 3+ Cells Content: Fibrinous Exudate present
Iris & Pupil	Round, Reactive	Iris Prolapse (Incarcerated in wound) Peaked Pupil deformity
Lens	Clear	Anterior Capsule Breached Traumatic Cataract (Rapid cortical opacification)

Abbreviations: **OD**: Oculus Dexter (Right Eye); **OS**: Oculus Sinister (Left Eye); **LogMAR**: Logarithm of the Minimum Angle of Resolution; **SUN**: Standardization of Uveitis Nomenclature.

The immediate post-operative course revealed a divergence from the expected trajectory of recovery, signaling a secondary pathology (Table 2). On day 1 post-operative, the eye exhibited a massive, hyper-acute inflammatory response. The anterior chamber reaction intensified to SUN Grade 4+ cells, accompanied by a dense fibrin membrane that obscured the pupil. The traumatic cataract progressed to total opacification. While such inflammation can be attributed to the surgical trauma, the intensity was disproportionate. On day 3 post-operative, despite 72 hours of broad-spectrum intravenous antibacterial therapy, the clinical picture deteriorated. A distinct, new morphological lesion appeared: a focal, creamy-white infiltrate developed adjacent to the corneal

suture line. Unlike bacterial infiltrates, which tend to be distinct and suppurative, this lesion exhibited irregular, feathery margins extending into the mid-stroma. This specific morphological appearance—feathery edges in the context of vegetative/metallic trauma—is highly predictive of a fungal etiology. It marked a diagnostic pivot point, shifting the working diagnosis from simple post-traumatic inflammation to secondary fungal keratitis.

To confirm this suspicion, a corneal scraping was performed immediately at the infiltrative edge. A potassium hydroxide (KOH) 10% wet mount was prepared and analyzed via light microscopy. The smear revealed the presence of hyaline, septate fungal hyphae. It is important to note the resource limitations

of the setting: fungal culture and polymerase chain reaction (PCR) speciation were unavailable. While this prevented the identification of the specific species (such as *Fusarium* vs. *Aspergillus*), the positive KOH smear combined with the clinical phenotype mandated an immediate change in therapeutic strategy.

The confirmation of fungal keratitis in a post-traumatic eye created a therapeutic dilemma: the inflammatory paradox. The eye required potent anti-inflammatory therapy to prevent phthisis from the fibrinoid reaction, yet steroids are traditionally contraindicated in fungal infections due to local immunosuppression. To navigate this, a dissociated therapeutic regimen was implemented; (1) Antifungal Strategy (The Ocular Surface Compartment): The infection was treated locally with aggressive monotherapy. Topical Natamycin 5% suspension was instilled every hour (q1h). Natamycin was selected as the polyene of choice because, unlike azoles, it possesses superior pharmacokinetic properties for penetrating the corneal stroma to target filamentous fungi. The hourly dosing was critical to maintain high drug concentrations within the tear film and anterior stroma, directly attacking the fungal biofilm; (2) Anti-inflammatory Strategy (The Systemic Compartment): To manage the destructive intraocular inflammation without compromising the corneal immune response, corticosteroids were administered systemically. The patient was started on oral Methylprednisolone at a dose of 24 mg per day. The dosage was strictly calculated based on the patient's body weight of 62 kg, resulting in approximately 0.4 mg/kg/day. This specific dosage was chosen as an intermediate window. It provides sufficient systemic anti-inflammatory potency to stabilize the blood-aqueous barrier and resolve the fibrinoid reaction. However, it remains below the 1 mg/kg/day threshold typically associated with profound systemic immunosuppression, thereby minimizing the risk of systemic fungal dissemination or inhibition of the host's global immune competence; (3) Supportive Therapy: Adjunctive medications were maintained to support the globe. Topical Moxifloxacin 0.5% was

continued every two hours to prevent bacterial superinfection of the compromised epithelium. Topical Atropine 1% was administered twice daily. This cycloplegic agent was essential to relieve ciliary spasm (pain control) and, more importantly, to keep the pupil dilated, preventing the formation of posterior synechiae between the iris and the inflamed lens capsule. Topical corticosteroids were strictly contraindicated. The protocol relied entirely on the physiological blood-tear barrier to prevent the systemic steroids from reaching the corneal surface in significant concentrations, thus allowing the Natamycin to work in a locally immune-competent environment. This dissociated approach—treating the infection topically and the inflammation systemically—aimed to decouple the immune response, allowing for the simultaneous salvage of the globe's structure and the eradication of the pathogen.

By Day 35, the globe was structurally stable with a healing paracentral leucoma. The anterior chamber was deep and quiet with 0 cells. Repeat corneal scrapings were negative for fungal elements. The final visual acuity improved to 6/45 (LogMAR 0.88). The primary limitation to further visual recovery was identified as the dense traumatic cataract. The patient was cleared for elective cataract extraction with intraocular lens implantation after a mandatory 3-month quiet period to minimize the risk of reactivation.

### 3. Discussion

The management of penetrating ocular trauma represents one of the most complex challenges in ophthalmic surgery, requiring a delicate balance between anatomical restoration and functional preservation.<sup>11</sup> However, the superimposition of a fungal infection upon an open-globe injury creates a severe, multifaceted pathology that fundamentally challenges standard treatment algorithms. This case report highlights the clinical utility of a physiology-based dissociated approach to medication delivery, offering a potential solution to a clinical scenario where adherence to traditional dogmas may result in

the loss of the eye. To understand the rationale for the therapeutic intervention, it is necessary to dissect the double hit phenomenon that characterizes this injury (Figure 1). The eye is an immune-privileged organ, a

status maintained by the tight junctions of the blood-retinal and blood-aqueous barriers, and an active suppression of inflammatory cascades to preserve optical clarity.<sup>12</sup>

Table 2. Diagnosis, treatment, outcome and follow-up.

TIMELINE	DIAGNOSIS & CLINICAL STATUS	THERAPEUTIC REGIMEN (The Dissociated Protocol)	
<b>Day 0</b> (Admission)	<b>Diagnosis:</b> Penetrating Ocular Injury with Iris Prolapse. <b>Clinical Status:</b> Open Globe, Hypotony. <b>Risk Factor:</b> Rusted metallic nail.	<b>Surgical</b> Primary Repair + Iris Abscission. <b>Systemic</b> IV Ceftriaxone 1g BID. <b>Topical</b> Moxifloxacin 0.5% (Intracameral).	<b>Anatomical Success:</b> Water-tight closure achieved (Seidel Negative).
<b>Day 3</b> (The Pivot)	<b>Diagnosis:</b> Fungal Keratitis (Secondary). <b>Findings:</b> Feathery infiltrate, KOH(+) Hyphae. <b>Inflammation:</b> Massive Fibrin, SUN Grade 4+.	<b>Protocol Initiated:</b> <b>Surface</b> Natamycin 5% <b>q1h</b> (Hourly). <b>Systemic</b> Oral Methylprednisolone <b>24mg/day</b> . <i>(Rationale: 0.4 mg/kg/day intermediate dose).</i>	<b>Objective:</b> Decouple surface infection from deep inflammation.
<b>Day 7</b>	<b>Status:</b> Early Response. Infiltrate density reduced. Fibrin resolving.	<b>Taper</b> Natamycin 5% <b>q2h</b> . <b>Maintain</b> Methylprednisolone <b>24mg</b> .	<b>AC Cells:</b> Reduced to SUN Grade 2+. <b>VA:</b> Hand Motion (Stable).
<b>Day 14 - 21</b>	<b>Status:</b> Consolidation. Epithelium healing. No new infiltrates.	<b>Taper</b> Natamycin <b>q4h → q6h</b> . <b>Taper</b> Methylprednisolone <b>16mg → 8mg</b> .	<b>AC Status:</b> Deep & Quiet. <b>Infiltrate:</b> Resolved to scar. <b>VA:</b> Improved to Counting Fingers (3m).
<b>Day 35</b> (Discharge)	<b>Diagnosis:</b> Healed Traumatic Fungal Keratitis with Leucoma. <b>Microbiology:</b> Repeat Smears Negative.	<b>Status Discontinued.</b> <b>Status Discontinued.</b>	<b>▲ VA: 6/45 (LogMAR 0.88).</b> <b>Anatomy:</b> Stable Globe, Quiet Eye. <b>Sequelae:</b> Dense Traumatic Cataract.
<b>Long-term</b>	<b>Strategy:</b> Mandatory Quiet Period (3 months) to minimize fungal reactivation risk before secondary intervention.		<b>Plan:</b> Elective Cataract Extraction + IOL.

Abbreviations: KOH, Potassium Hydroxide; SUN, Standardization of Uveitis Nomenclature; VA, Visual Acuity; IOL, Intraocular Lens; q1h, Every hour; q2h, Every 2 hours; BID, Twice daily (bis in die); IV, Intravenous; AC, Anterior Chamber; LogMAR, Logarithm of the Minimum Angle of Resolution. Note: The Dissociated Protocol refers to the separation of systemic anti-inflammatory therapy from topical antimicrobial therapy to leverage the blood-tear barrier.

The first hit was traumatic disruption and the cytokine storm. Penetrating trauma catastrophically disrupts this immune privilege. The initial mechanical injury causes an immediate breakdown of the blood-aqueous barrier, allowing protein-rich fluid and leukocytes to flood the anterior segment. This is not merely a passive leak but an active, biologically aggressive response.<sup>13</sup> The injury triggers a cytokine storm, characterized by the acute release of pro-inflammatory mediators such as Interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), and

prostaglandins. While this inflammatory response is evolutionarily designed to facilitate wound healing and seal the globe, in the confined anatomy of the eye, unchecked inflammation is maladaptive. The resulting fibrin deposition acts as a scaffold for fibroblast proliferation, which can lead to the formation of cyclitic membranes, tractional retinal detachment, and phthisis bulbi (atrophy of the globe). Thus, the first hit creates a biological imperative for immunosuppression to preserve the eye's architecture.

The introduction of fungal elements acts as a lethal second hit. Fungal pathogens, particularly filamentous types such as *Fusarium* and *Aspergillus* species common in tropical climates, are not passive colonizers.<sup>14</sup> They possess sophisticated virulence factors. These fungi secrete matrix metalloproteinases (MMPs) and other proteolytic enzymes that actively digest corneal collagen, further weakening the structural integrity of an already compromised globe. Furthermore, fungi trigger a distinct immune pathway, primarily

recruiting neutrophils to the site of infection. While neutrophils are essential for attacking fungal hyphae, their excessive accumulation leads to bystander damage. The release of reactive oxygen species and lysosomal enzymes by neutrophils can cause rapid stromal melting, accelerating corneal perforation. This creates a hostile pathological environment where the host's immune response is simultaneously necessary for survival (to kill the fungus) and detrimental to the outcome (melting the cornea and scarring the uvea).<sup>15</sup>



Figure 1. Pathophysiology of the combined injury.

The central teaching point of this case is the management of the resulting inflammatory paradox. The clinician is faced with a binary choice, both of which carry high risks.<sup>16</sup> Standard protocols for fungal keratitis strictly mandate the cessation of all corticosteroids. Corticosteroids suppress the macrophage and neutrophil responses essential for fungal clearance and, in many cases, enhance fungal replication. Conversely, in the context of severe penetrating trauma, withholding steroids allows the fibrinoid syndrome to proceed unchecked, leading to phthisis bulbi and the permanent loss of the globe.<sup>17</sup> Our approach resolved this dilemma by utilizing the principle of pharmacokinetic compartmentalization. We hypothesized that we could decouple the treatment of the infection from the treatment of the inflammation based on the route of administration. By using topical Natamycin 5% drops, we achieved extremely high drug concentrations on the ocular surface and in the anterior stroma. Natamycin is a polyene antifungal that works by binding to ergosterol in the fungal cell membrane. By applying it hourly, we maintained a lethal concentration directly at the site of the fungal biofilm. Simultaneously, by administering Methylprednisolone orally, we relied on the systemic circulation to deliver the anti-inflammatory agent. Systemic drugs reach the eye via the ciliary circulation, which perfuses the vascular uveal tissues (iris and ciliary body). This allowed us to treat the traumatic iridocyclitis effectively.

The success of this regimen relies on a specific physiological barrier: the blood-tear barrier. Crucially, systemic corticosteroids result in significantly lower corneal tear film concentrations compared to topical drops. The tight junctions of the lacrimal gland and the corneal epithelium prevent the bulk of systemically administered drugs from diffusing into the precorneal tear film. Pharmacokinetic studies suggest that while systemic steroids can effectively penetrate the aqueous humor (thereby treating the internal uveitis and suppressing fibrin), their concentration in the corneal epithelium—where the fungus resides—is negligible compared to direct topical application. This creates a

therapeutic window: it allows for the suppression of potentially blinding intraocular inflammation (preventing synechiae and pain) while sparing the localized corneal surface immunity. This dissociated delivery ensures that the macrophage response required to clear the fungal hyphae on the surface is not inhibited by the steroids treating the interior of the eye.

It is imperative to distinguish this approach from the use of topical steroids, which remains contraindicated. The literature clearly demonstrates the failure of topical steroids in fungal keratitis. The landmark mycotic ulcer treatment trial (MUTT) provided robust evidence that the adjunctive use of topical steroids in fungal corneal ulcers is deleterious. The trial outcomes reinforced that topical application delivers a massive steroid load directly to the site of infection, which delays epithelial healing, increases the risk of corneal perforation, and worsens visual outcomes.<sup>18</sup>

Our case contrasts with the MUTT findings because the route of administration was systemic, not topical. This dissociation is critical; topical application creates a local immunocompromised zone directly on top of the reproducing pathogen. In contrast, systemic application modulates the global inflammatory environment via the vasculature, suppressing the destructive cytokine storm without paralyzing the local surface defenses. This distinction aligns with emerging, albeit limited, evidence suggesting that systemic steroids may be safer than topical steroids in complex infective keratitis cases where structural integrity is at risk.

The management of the lens in this case also required a nuanced strategy. The development of the traumatic cataract was likely multifactorial, involving the direct mechanical shock of the injury, the breach of the lens capsule, and the metabolic disturbance caused by the severe inflammation. A critical consideration in fungal trauma cases is the phenomenon of fungal sequestration. The lens capsule, once breached, can act as a reservoir for fungal elements. Fungi can remain dormant within the

lens material, protected from both the host immune system and topical antifungal agents. Consequently, performing cataract surgery during the active phase of infection carries a high risk of endophthalmitis. The manipulation of the lens could release sequestered fungal spores into the vitreous cavity, converting a localized keratitis into a devastating endophthalmitis. Our strategy of observing a strict waiting period—ensuring the corneal smear was negative, and the eye was quiet for three months—aligns with best practices. This interval allows for the sterilization of the anterior segment and the stabilization of the blood-aqueous barrier, minimizing the risk of reactivating sequestered fungi during future phacoemulsification.<sup>19</sup>

While the outcome of this case was favorable, several limitations must be acknowledged to provide a balanced scientific perspective. The primary limitation is the lack of fungal culture and speciation. The diagnosis relied solely on clinical morphology and a potassium hydroxide (KOH) smear. Without culture-confirmed speciation, we cannot definitively state whether the pathogen was truly susceptible to Natamycin or if the host immunity played a larger role in the clearance. In a resource-rich setting, polymerase chain reaction (PCR) diagnostics would be the gold standard to guide targeted antifungal therapy. As a single case report, the findings have limited generalizability and are inherently subject to selection bias, as successful outcomes are more likely to be written up and published than failures. This protocol represents a proof-of-concept rather than a validated clinical guideline. The reported follow-up of 35 days, while sufficient to document the resolution of the acute infection and inflammation, is relatively short. Fungal keratitis is notorious for latency; late recurrences have been documented months after apparent clinical cure. Long-term monitoring is essential to confirm true eradication.<sup>20</sup>

#### 4. Conclusion

The management of penetrating ocular trauma complicated by fungal keratitis remains one of the

most unforgiving scenarios in ophthalmology, often forcing clinicians into a therapeutic paralysis where the treatment for one pathology exacerbates the other. This case report challenges the traditional binary approach to corticosteroid use in fungal infections. We conclude that the presence of secondary fungal keratitis in penetrating ocular trauma does not necessitate the complete abandonment of anti-inflammatory therapy. Instead, it calls for a precise, physiology-based strategy. The dissociated therapeutic regimen described herein—coupling aggressive topical antifungals (Natamycin) with calculated, intermediate-dose systemic corticosteroids—offers a viable strategy to decouple the treatment of infection from the treatment of inflammation.

This approach theoretically leverages the physiological blood-tear barrier to protect the ocular surface immunity, allowing the antifungal agent to work effectively, while simultaneously managing the destructive intraocular fibrinoid response via the systemic circulation. By respecting the distinct pharmacokinetic compartments of the eye, clinicians can potentially salvage globes that present with this devastating dual pathology. While this protocol requires further validation through larger cohorts with confirmed culture speciation, it provides a logical, scientifically grounded framework for navigating the inflammatory paradox and preserving vision in complex ocular trauma.<sup>20</sup>

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