Case Report

# Combination of Intracameral and Intrastromal Voriconazole in the Treatment of Recalcitrant *Acremonium* Fungal Keratitis

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## ABSTRACT

We present a report of a 28-year-old female with fungal keratitis due to *Acremonium* that was unresponsive to full medical therapy over 3 weeks. The patient was treated with superficial keratectomy, intrastromal and intracameral voriconazole injections. There was a marked clinical improvement beginning on day 3 post-therapy that was sustained until the last follow-up at 6 months. This is the first case of fungal keratitis due to *Acremonium* treated by a combination of intrastromal and intracameral voriconazole. This cost-effective treatment modality proved to be significant in impeding the progression of this potentially blinding disease and improving visual prognosis.


**Key words:** *Acremonium*, Fungal keratitis, Intracameral Injection, Intrastromal Injection, Voriconazole


**Access this article online**

**Website:** www.meajo.org

**DOI:** 10.4103/0974-9233.95271

**Quick Response Code:**


## INTRODUCTION

Fungal keratitis is a leading cause of monocular blindness worldwide with a reported incidence varying from 6 to 50% and a tendency to significantly increase in tropical climates.[1] Predisposing factors to the infection include trauma with organic matter, long-term use of broad-spectrum antibiotics and topical steroid, corneal surface disorders, refractive surgery and specific contact lens disinfectant solutions.[2]

The most common filamentous fungi that cause keratitis are *Fusarium* and *Aspergillus*. In this article we report a case of keratomycosis with an unusual organism, *Acremonium*. *Acremonium* is a filamentous cosmopolitan fungus mostly isolated from plant debris, soil, and heating ventilation air conditioning systems in building materials. Fungal keratitis due to *Acremonium* after laser *in situ* keratomileusis (LASIK) and nonsurgical trauma to the cornea has been previously reported.[3]

This case report demonstrates the safe use of intrastromal and intracameral voriconazole injections in the treatment of filamentous fungal keratitis.

## CASE REPORT

A 28-year-old female presented 2 weeks after sustaining injury to her right eye by a blow containing dust. A cosmetic contact lens was in place at the time of trauma and was removed a few hours later. At presentation, she had decreased visual acuity (20/100) and a painful red eye. The patient was already treated with topical ciprofloxacin and a combination of tobramycin/dexamethasone eyedrops along with PO amoxicillin. On examination, the patient had a corneal ulcer with +3 conjunctival injection, a large epithelial defect with underlying thick whitish infiltrates and +4 anterior chamber cells. Cornea cultures were sent for microbiological investigation including potassium hydroxide (KOH) wet-mount preparation, Gram stain, and cultures on blood agar, chocolate agar, and Sabouraud's dextrose agar.

The patient was initially treated with fortified vancomycin

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(50 mg/ml), amikacin (33 mg/ml), and amphotericin B (1 mg/ml). Although the pain decreased, the vision continued to deteriorate to count fingers at 1 m and a corneal melt began. After 5 days, fungal culture contained *Acremonium* species identified by microscopic and morphological features based on Sabouraud and fungisel agar. Unfortunately, subspeciation of the organism and its antimicrobial sensitivity could not be assessed in our microbiology laboratory.

Oral voriconazole was our first choice for treatment but was declined by the patient due to financial constraint. The patient was advised to begin topical voriconazole 1% hourly and sporanox PO 400 mg QD. Despite maximal medical treatment, the cornea was melting with impending perforation and an anterior chamber hypopyon was rapidly forming [Figure 1]. We believed that the topical treatment was not reaching therapeutic concentrations in the cornea. Hence, we planned superficial therapeutic keratectomy along with intrastromal and intracameral injection of voriconazole (50 $\mu$g/0.1 ml) due to the rapidly deteriorating condition and involvement of the anterior chamber. The injection was prepared using the method described by Prakash *et al*.[4] Voriconazole (VFEND; Pfizer Inc, NY) is available as 200 mg of white lyophilized powder in a glass vial. It was reconstituted with 19 ml of lactated ringer solution (LR) to obtain 20 ml of clear concentrate containing 10 mg/ml of voriconazole. An aliquot of 1 ml of this solution was diluted with 20 ml of LR to a concentration of (50 $\mu$g/0.1 ml). An informed consent was signed by the patient. In the operating room and under aseptic conditions, superficial therapeutic keratectomy was performed and cultures specimens were acquired from the intrastromal bed and from aqueous fluid. Using a 1-ml tuberculin syringe attached to a 30-G needle, 0.07 ml of voriconazole (50 $\mu$g/0.1 ml) was injected intrastromally around the area of the ulcer. The amount of hydration of the cornea was used as a guide to assess the area covered. Similarly, 0.05 ml of voriconazole (50 $\mu$g/0.1 ml) was injected intracamerally. Corneal cultures were positive for *Acremonium* species while the culture from the aqueous tap was negative.

Postoperatively, the patient was maintained on topical amphotericin B, voriconazole 1% Q 1 hour and sporanox 400 mg PO QD. Three days postinjection, there was a significant decrease in eyelid edema, ocular pain, hypopyon and the epithelial defect [Figure 2]. Her vision was still HM due to a pupillary inflammatory membrane blocking the visual axis. Six weeks later, her vision improved to CF at 3 m and the epithelial defect continued to resolve with a significant decrease in the cellular infiltrates and complete resolution of the anterior chamber reaction. However, the pupillary membrane remained. Six months later, the vision improved to 20/100 post-dilation with a quiet eye, a thin central corneal scar and marked reduction in corneal vascularization [Figure 3].

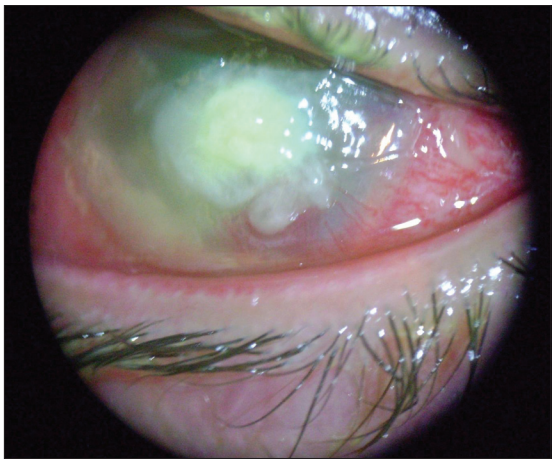

**Figure 1:** Corneal ulcer and corneal melt induced by fungal infection

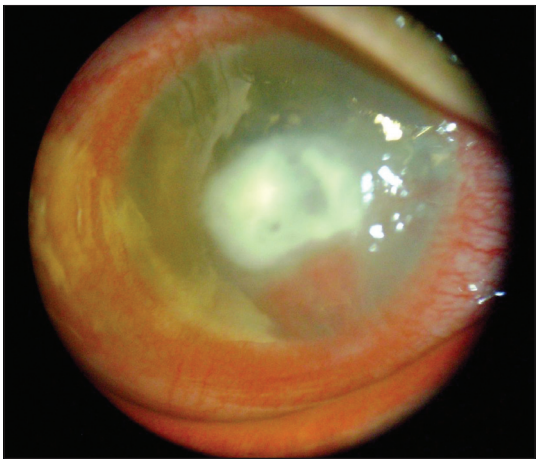

**Figure 2:** Three days postintrastromal voriconazole injection

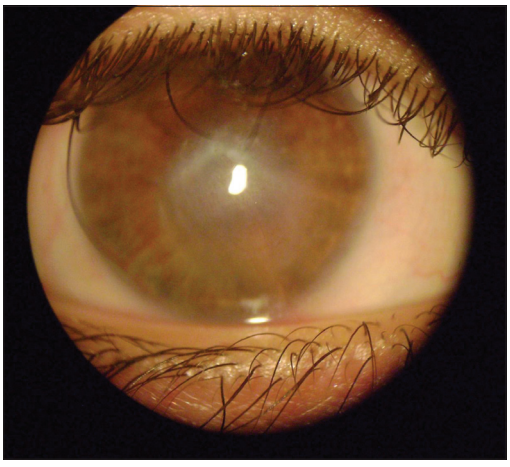

**Figure 3:** Healed corneal ulcer at 6 months

## DISCUSSION

Several drugs have been used to treat filamentous fungal corneal ulcers. Natamycin is the most commonly used topical

treatment followed by amphotericin. However, resistance to amphotericin B is increasing.[5,6] Itraconazole and voriconazole are the most frequently used systemic treatments for filamentous ulcers although the latter is the preferred topical treatment in an ideal world.[7] Surgical intervention (such as keratoplasty, evisceration, or enucleation) is necessary in 15–27% of patients, due to advanced keratitis, failed medical therapy and progressive thinning with impending perforation.[6,8]

Numerous case reports indicate that voriconazole has been successful when amphotericin B or fluconazole have been unsuccessful, even in cases of drug-resistant fungal keratitis and endophthalmitis.[9-11] Voriconazole, a second-generation triazole derived from fluconazole, offers broad-spectrum activity against various fungi affecting the eye. It primarily inhibits the cytochrome P450 14-alpha demethylase and 24-methylene dihydrolanasterol demethylation in certain yeasts and filamentous fungi. It has a molecular mass of 349.32 Da that allows good corneal penetration,[12] and therefore better ocular bioavailability.

Oral voriconazole has good intraocular penetration with therapeutic levels of the drug achieved in aqueous (1.7 $\mu$g/mL) and in vitreous (1.5 $\mu$g/mL).[13] However, oral voriconazole is expensive and can cause systemic side effects such as transient visual disturbances, facial erythema, and elevated liver enzymes.[14] Animal studies demonstrated effectiveness in ocular penetration when administered topically.[15] In humans, topical voriconazole was shown to have good corneal epithelial penetration requiring minimal need to rescrape the epithelium.[5,16] Aqueous voriconazole concentration can reach up to (6.5 $\mu$g/mL) after topical use exceeding the level achieved by oral administration.[17] In a human study, 85-90% of the drug was absorbed into the aqueous humor with topical use compared to 53% oral administration.[18] To achieve sustained high levels for effective antifungal therapy in corneal keratitis, voriconazole should be topically administered every 30 minutes.[19]

Intraocular use of voriconazole in treating fungal keratitis is an off-label use. This modality of treatment might be used in severe cases of fungal keratitis where higher intraocular concentration of the drug is warranted to eradicate the organism. The experimental use of intravitreal voriconazole injections in rodents proved to be safe with no electroretinographical or histopathological abnormalities.[20] The experimental use of intracameral voriconazole in humans showed no toxic effects when the aqueous concentration was (10 $\mu$g/mL - 1.5 mg/mL).[21] Above 1.5 mg/mL there was a dose-dependant reduction in corneal endothelial cells, trabecular meshwork cells, and retinal pigment epithelial cells.[21]

Intrastromal administration of voriconazole might be a safe and cost-effective method of providing higher concentration of the drug when there is a risk of corneal melt and perforation. Intrastromal injection of (0.05 – 0.1 ml) of voriconazole (50 $\mu$g/0.1 ml) aided in the resolution of different fungal infections.[4] Repeated intrastromal injections of voriconazole (50 $\mu$g/0.1 ml) were tolerated with no long-term ocular toxicity noted.[22] Intrastromal injections of 0.1 ml of voriconazole (25 $\mu$g/ml) have also been used to treat *Acanthamoeba* keratitis with no complications.[23]

In the current case, after 3 weeks of topical and oral antifungal treatment, there was clinical deterioration of the corneal ulcer and the culture from the corneal scraping taken in the operating room remained positive and grew *Acremonium*. Several factors might hamper ocular penetration of the drug through topical use including the thickness of the cornea and the pathogen load. This is the first case report in English peer review literature to treat *Acremonium* species with the combination of intrastromal and intracameral voriconazole. This medical therapy was safe, allowing higher drug bioavailability within the anterior chamber thus controlling the corneal and intraocular infection compared to topical use. However, clinical trials assessing the safety and efficacy of intrastromal and intracameral voriconazole should be considered.

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**Cite this article as:** Haddad RS, El-Mollayess GM. Combination of intracameral and intrastromal voriconazole in the treatment of recalcitrant acremonium fungal keratitis. Middle East Afr J Ophthalmol 2012;19:265-8.

**Source of Support:** Nil, **Conflict of Interest:** None declared.