Adv Ther (2024) 41:3316–3327
https://doi.org/10.1007/s12325-024-02929-3

ORIGINAL RESEARCH

Treatment Strategies for Filamentous Fungi Keratitis

Julia Storr · Daniel Zapp · Nathalie Bleidißel · Christian S. Mayer · Mathias M. Maier · Kathrin Rothe

Received: May 21, 2024 / Accepted: June 13, 2024 / Published online: July 3, 2024

ABSTRACT

Introduction: This research aims to describe clinical findings, epidemiology and treatment outcomes in patients with filamentous fungi keratitis of a tertiary centre in Germany over a 7-year period and to compare the efficacy of different antifungal treatments and the effect of additive topical steroids.

Methods: This retrospective study included 25 eyes of 23 patients from October 2013 to December 2020 with cultural isolates of filamentous fungi and corresponding keratitis. Best-corrected visual acuity (BCVA), clinical signs, symptoms, risk factors and outcome were extracted from medical records.

Results: Improvement of BVCA was noted in 68% of eyes. Mean BCVA of the study population increased from 0.75 logMAR [median 0.40, standard deviation (SD) 0.82, range 0–2.3] to 0.48 logMAR (median 0.10, SD 0.88, range – 0.1 to 3). The most commonly used antifungal topical treatment was a combination of natamycin 5% and voriconazole 2% (44% of eyes), followed by voriconazole 2% in 36% of cases. An antiinflammatory topical steroid was applied in 52%. In 16% of the eyes, penetrating keratoplasty (pKP) was performed.

Conclusion: Diagnosis of filamentous fungi keratitis is often difficult or delayed. Outcomes can be poor even with intensive treatment because of high resistance to common antifungals. Access to natamycin 5% seems to lead to favourable outcomes in filamentous fungi keratitis.

Keywords: Filamentous fungi; Natamycin; Fusarium keratitis; Keratomycosis; Cornea; Infection

Julia Storr and Daniel Zapp contributed equally to this work.

J. Storr (✉) · D. Zapp · N. Bleidißel · M. M. Maier
Department of Ophthalmology, Klinikum Rechts der Isar, Technical University Munich (TUM), Ismaningerstr. 22, 81675 Munich, Germany
e-mail: julia.storr@mri.tum.de

C. S. Mayer
Department of Ophthalmology, Ortenau Klinikum Offenburg-Kehl, Offenburg, Germany

K. Rothe
Department of Medical Microbiology, Immunology and Hygiene, Technical University Munich (TUM), Munich, Germany

Key Summary Points

Why carry out this study?

Filamentous fungi keratitis is a rare disease which can lead to poor functional outcomes if treatment is late or inadequate.

This study seeks to compare antifungal treatments and evaluate time to diagnosis, the role of topical steroids, as well as surgical intervention.

What was learned from the study?

Best-corrected visual acuity (BCVA) improvement is significantly better without surgical intervention. Penetrating keratoplasty (pKP), while necessary in some cases, leads to a significantly poorer outcome.

Improvement of visual acuity was significantly worse the longer the time from onset of symptoms to presentation was. BCVA improvement was also significantly reduced after a longer diagnosis interval.

Delayed diagnosis after presentation was associated with worse visual outcome.

INTRODUCTION

Filamentous fungi keratitis is a global sight-threatening corneal infection, which can lead to poor visual outcomes if left untreated or recognized too late [1]. Early identification of pathogen is key to obtaining good outcomes.

The incidence of fungal keratitis has been reported as 0.02/100,000 in Europe and 33.9/100,000 in Asia [2]. Concrete numbers for Germany have been difficult to obtain. To analyse epidemiological data the German Register for Fungal Keratitis was established in 2015 by the National Reference Center for Invasive Fungal Infection (NRZMyk) and the department of ophthalmology of the university hospital Düsseldorf. Thus, important information on fungal keratitis can be collected, by direct reports of fungal keratitis from other eye clinics, or by positive fungal cultures through the NRZMyk [3]. As of January 2018, 102 cases of fungal keratitis had been reported, among those 37% *Fusarium* spp. and 6% *Aspergillus* spp. [4].

Filamentous fungi keratitis most commonly occurs in warm and humid tropical and subtropical regions. Trauma with organic material has been identified as a risk factor, commonly related to agricultural work [5]. It has been postulated that the incidence of mycotic keratitis is inversely proportional to the distance from the equator, with higher numbers the closer one is to the equator [6]. But even in more temperate regions, incidence of mycotic keratitis is increasing. With rising temperatures due to climate change, it is possible that numbers will continue to grow in northern regions, making access in Germany to effective treatment all the more important [2].

A possible reason for increasing numbers could also be a rise in the use of contact lenses. Important to note is the international outbreak of contact lens-associated fusarium keratitis from 2004 to 2006, related to "ReNu with Moisture Loc" contact lens solution by Bausch & Lomb [7].

Other risk factors are preceding ocular surgery, immunosuppressive diseases and medication, as well as topical steroid treatments. Preceding herpes keratitis and the abuse of local anaesthetics can also cause filamentous fungi keratitis [3].

Clinical symptoms and signs for fungal keratitis are vision loss, epiphora, photophobia and pain. Classic signs during slit lamp examination are a prominent corneal infiltrate or ulcer with raised epithelial slough, feathery serrated margins and satellite lesions [8]. The colour of the infiltrates is usually greyish-white with a potential epithelial defect or initially closed epithelium. A stromal-endothelial immunological reaction can occur, with conjunctival injection and chemosis [9]. In case of intraocular inflammation, a hypopyon is often pyramid-convex shaped [10].

Even though not all of these clinical signs are required for a correct diagnosis, a study from 2005 showed that if all of these criteria are met, the probability for fungal infection was 83% [11].

The aim of this study was to compare the efficacy of different antifungal treatments, as well as to analyse the effect of additive topical steroids. The goal was to provide an updated view on filamentous fungi keratitis management in Germany.

METHODS

A monocentric retrospective study was conducted at the department of ophthalmology of the university hospital rechts der Isar of the Technical University of Munich, Germany. The university's ethics committee granted approval for this study (738/20 S-EB). This type of study does not require informed consent. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

After reviewing the records of all patients who presented to our clinic from December 2013 until October 2020 with cultural isolates of filamentous fungi from corneal swabs, scrapings and contact lens containers, we excluded those who did not express clinical signs of fungal keratitis. We furthermore excluded those who presented with keratitis, but were not treated with antifungal medication, judging those as accidental contamination. We enrolled 25 eyes of 23 patients in this study. Epidemiological data, risk factors, clinical signs and treatment were identified from patient records.

Best-corrected visual acuity (BCVA) was measured at first presentation and last presentation to our clinic with Snellen charts using European norm DIN EN ISO 8596. Non-numeric values, such as counting fingers, hand movement, light perception and no light perception, were assigned numeric values. Final presentation was determined when no signs of infection or activity were present.

Corneal swabs, scrapings and contact lens material, if available, were sent to the university clinic's department of microbiology for testing. Inoculation on Sabouraud agar is considered the golden standard for fungal cultures [12].

To aid in early detection of fungal pathogens, even before cultural isolates, in vivo confocal microscopy (IVCM) can be used to identify filamentous fungi. IVCM in our clinic is performed using the HRT II with Rostock Cornea Module (RCM) for confocal scanning laser microscopy by Heidelberg Engineering (Heidelberg Engineering, Heidelberg, Germany). Through direct contact microscopy under local anaesthesia a two-dimensional image of a 400×400 µm area was taken, measuring 384×384 pixels [13]. Depending on the experience of the examiner, it is possible to differentiate between different filamentous fungi species [14].

Anterior segment optical coherence tomography (AS-OCT) is a non-invasive non-contact method for quantitative analysis in fungal keratitis. It is possible to measure the width and depth of corneal infiltrates, as well as corneal thickness.

For statistical analysis and illustration creation IBM SPSS Statistics (version 28.0.0.0, SPSS Inc.) and Excel (version 16.73, Microsoft) were used. Decimal values were converted to logMAR equivalents. Descriptive statistics were used for categorical variables, while continuous variables were displayed as mean ± standard deviation (SD) or median and range. To estimate the precision of our results, we calculated 95% confidence intervals. These intervals indicate the range within which the true value is expected to lie with a probability of 95%. Statistical tests, such as Spearman correlation, Pearson correlation, Mann–Whitney *U* test and chi-square test were used. *P* values < 0.05 were considered statistically significant.

RESULTS

Twenty-five eyes from 23 consecutive patients, with two patients suffering from bilateral keratitis, were included. More than two-thirds of patients were female ($n = 16$, 70%). The median age was 42 years (range 19–75 years). In 56% of cases the left eye was affected ($n = 14$). Overall, 43% of patients ($n = 10$) were from rural areas. The noted symptoms were pain ($n = 17$, 74%), conjunctival injection ($n = 7$, 30%), foreign body sensation ($n = 6$, 26%), photophobia ($n = 5$, 22%), epiphora ($n = 4$, 17%) and vision loss ($n = 2$, 9%).

Predisposing risk factors were found in 96% of patients ($n=22$). Overall, 70% of patients ($n=16$) acknowledged regular contact lens wear, exclusively soft contact lenses, those with bilateral keratitis being affected. Other predisposing factors included preceding topical steroid treatment ($n=12$, 48%), trauma with biological material ($n=5$, 22%), prior keratitis ($n=4$, 17%), preceding ocular surgery (one penetrating keratoplasty (pKP) for a corneal scar and one laser refractive surgery) ($n=2$, 9%), as well as immunosuppressive diseases in two cases (9%) (Table 1).

Table 1 Characteristics of the affected eyes ($n=25$)

Baseline characteristics	
Age (mean, in years)	41.2
Female gender	16
Left eye	14
Urban origin	13
Clinical signs	
Central location of infiltrates	14
Number of infiltrates	1–6
Hypopyon	6
Epithelial defect	21
Perforation	0
Risk factors	
Prior ocular surgery	2
Prior keratitis	4
Prior ocular trauma with organic material	5
Prior steroid treatment	12
Contact lens wear	18
Diabetes mellitus	1
Neurodermitis	1
Prior herpes zoster	1
No risk factors	1
Diagnostics	
In vivo confocal microscopy	4
Anterior segment optical coherence tomography	12

The mean time from onset of symptoms to presentation in our clinic was 6.92 days (±7.08 days, 95% CI 4.00–9.84, range 1–21 days). Improvement of visual acuity was significantly worse the longer the time from onset of symptoms to presentation ($r=0.58$, $p>0.005$). Visual acuity improvement was also significantly reduced after a longer diagnosis interval ($r=0.41$, $p>0.05$). The mean time from first presentation to correct diagnosis was 6.96 days (±12.28 days, 95% CI 1.89–12.03, range 0–58 days). Delayed diagnosis after presentation was associated with worse visual outcome ($r=0.44$, $p>0.05$). The mean time from onset of symptoms to correct diagnosis was 13.88 days (±17.50 days, 95% CI 6.66–21.10, range 1–79 days).

Most common clinical findings were an epithelial defect in 21 eyes (84%), as well as a centrally located corneal infiltrate in 56% of cases ($n=14$); 21% of eyes ($n=6$) presented with a hypopyon (Fig. 1). No corneal perforation was noted at first presentation.

The most common aetiological agent in central infiltrates was *Fusarium* spp. in nine cases (64.3%), followed by *Aspergillus* spp. and *Scedosporium apiospermum* in two eyes (14.3%), respectively. Visual improvement was not significant for eyes with central infiltrates, compared to eyes with peripheral infiltrates ($p>0.05$). However, eyes with centrally located infiltrates showed significantly worse BCVA

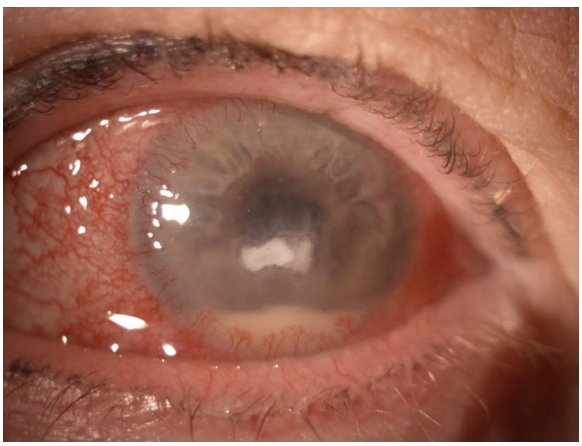

Fig. 1 Clinical signs of filamentous fungi keratitis: prominent corneal infiltrate with feathery margins, epithelial slough and convex hypopyon

at presentation (1.15 logMAR) compared to eyes with peripheral infiltrates (0.24 logMAR, $p<0.01$).

A majority of eyes ($n=18$, 72%) presented with one corneal infiltrate, 20% ($n=5$) with two. In one eye (4%), four infiltrates were found, in another (4%) six infiltrates.

Filamentous fungi were most commonly isolated from contact lens materials ($n=11$, 44%), followed by corneal scrapings ($n=9$, 36%) and corneal swabs ($n=5$, 20%). *Fusarium* spp. made up for the majority of cases ($n=14$, 56%). *Aspergillus fumigatus* was the second most common pathogen ($n=5$, 20%). In 12% of eyes *Purpureocillium lilacinum* ($n=3$) was the causal agent of fungal keratitis, followed by *S. apiospermum* in two cases (8%). The smallest group was *Alternaria hordeicola,* found in one eye (4%). Closer differentiation between *Fusarium* spp. showed *Fusarium oxysporum* ($n=4$, 16%), *Fusarium solani* ($n=3$, 12%), *Fusarium dimerum* ($n=3$, 12%), *Fusarium napiforme* ($n=2$, 8%), *Fusarium falciforme* ($n=1$, 4%) and *Fusarium petroliphilum* ($n=1$, 4%). In two cases, no closer differentiation was possible.

A total of 24 eyes (96%) had been treated with topical antibiotics at the time of presentation. Only four eyes (16%) had received antifungal medication. The most common medication at presentation was a combination of topical antibiotics and steroids ($n=9$, 36%); 48% of cases ($n=12$) were pretreated with topical steroids. BCVA improvement was significantly higher in eyes without prior steroid treatment ($p<0.005$). Eyes with prior steroid treatment suffered BCVA deterioration from a mean 0.44 logMAR to 0.77 logMAR, while eyes without steroid treatment improved from 1.0 logMAR to 0.22 logMAR. Eyes without prior steroid treatment had better BCVA at presentation (0.44 logMAR) than eyes without (1.03 logMAR), though it was not statistically significant ($p=0.07$).

We performed IVCM in four cases (16%) and AS-OCT in 12 cases (48%) (Figs. 2, 3).

The mean time of treatment was 75.40 days (± 60.08 days, 95% CI 50.60–100.20, range 7–232 days). The worse BCVA was at presentation, the longer the treatment duration ($r=0.400$, $p>0.05$). In 64% of cases ($n=16$) patients were admitted to the hospital for

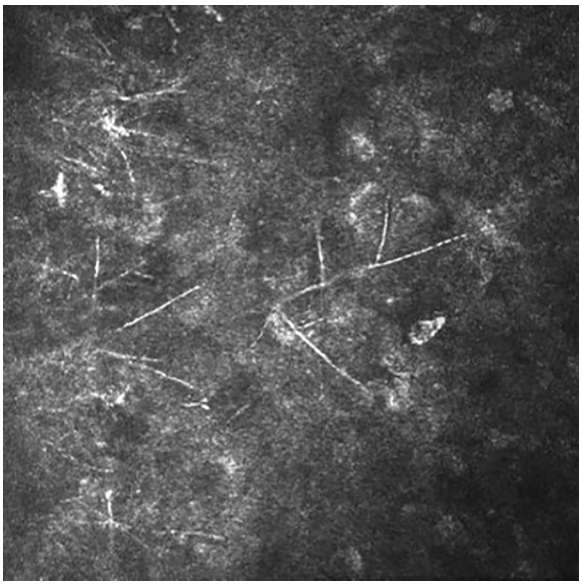

Fig. 2 In vivo confocal microscopy (IVCM) of *S. apiospermum* hyphae

in-patient treatment for 14.44 days (± 14.31, 95% CI 6.81–22.06, range 2–58 days). In-patient treatment was longer the longer the delay between first presentation and diagnosis ($r=0.50$, $p=0.05$), as well as the longer the delay between onset of symptoms and diagnosis ($r=0.51$, $p>0.05$).

Topical antifungal medication was either a combination of natamycin 5% and voriconazole 2% ($n=11$, 44%) or a single treatment of voriconazole 2% ($n=9$, 36%). Two eyes (8%) received a triple treatment of voriconazole 2%, natamycin 5% and amphotericin B 0.5%. One eye (4%), respectively, was treated with either natamycin 5% or amphotericin B 0.05% or a combination of voriconazole 2% and amphotericin B 0.05% (Fig. 4).

An anti-inflammatory therapy with topical steroids was added after a mean time of 8.62 days (± 8.6 days, 95% CI 3.43–13.81, range 1–31 days) after starting antifungal medication in 13 cases (52%). BCVA at presentation was worse in eyes which received additive topical steroids (0.85 logMAR) than eyes without additive topical steroids (0.64 logMAR). BCVA at last presentation, however, was better in eyes with additive steroid treatment (0.41 logMAR) than in eyes without additive steroid treatment

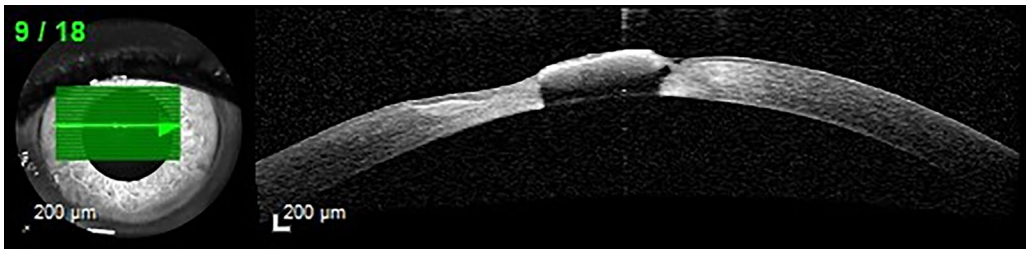

Fig. 3 Anterior segment optical coherence tomography (AS-OCT) of a prominent corneal infiltrate (*A. fumigatus*) with epithelial defect

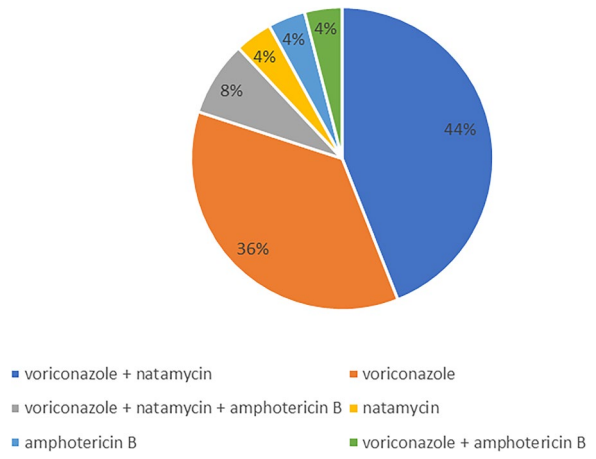

Fig. 4 Topical antifungal medication. Most common was a combination of voriconazole and natamycin ($n=11$, 44%), followed by voriconazole as monotreatment ($n=9$, 36%)

(0.57 logMAR). The difference in visual acuity was not statistically significant ($p>0.05$).

Fourteen cases (56%) received 400 mg voriconazole daily. Systemic treatment lasted for a mean time of 37.43 days (±35.04, 95% CI 17.20–57.66, range 7–122 days). There was no significant difference in BCVA improvement for cases with oral treatment compared to eyes without oral treatment ($p>0.05$).

Surgical management involving amnion membrane transplantation was performed in four eyes (16%), as well as pKP in four eyes (16%). Eyes with pKP had significantly worse visual outcome (deterioration of 1.03 logMAR) than eyes without (improvement of 0.51 logMAR, $p>0.05$). There was no need for enucleation in any case.

Mean BCVA of all cases at first presentation was 0.75 logMAR (±0.82, range 0–2.3 logMAR), with a mean improvement at last presentation to 0.48 logMAR (±0.88, range – 0.1 to 3) (Fig. 5). Regarding visual acuity, 17 eyes (68%) had a good outcome, 4 eyes (16%) remained stable, and 4 eyes (16%) had a poor outcome. Mean BCVA improvement was –0.26 logMAR (±1.03, 95% CI – 0.69 to 0.16).

Complications were secondary glaucoma in 2% of cases ($n=5$), 16% ($n=4$) cataract, phthisis bulbi ($n=1$, 4%), persistent epithelial defects in three eyes (12%), and corneal perforation in two eyes (8%).

DISCUSSION

Filamentous fungi keratitis is a rare but aggressive disease that is extremely difficult to treat and can lead to very poor functional outcomes and even blindness [3].

The most common pathogen detected in this study was *Fusarium* spp. with 56% of affected eyes, followed by *Aspergillus* spp. with 20%, similar to other studies [15]. In countries with temperate climates, fungal keratitis accounts for a relatively small proportion of infectious keratitis (1–10%), whereas in the tropics and subtropics, a large proportion of keratitis (40%) is mycotic in origin [4]. Male agricultural workers in tropical areas are frequently affected, with trauma from organic material being a risk factor [3, 6, 9]. In tropical regions, *Fusarium* spp. is most frequently responsible for filamentous fungi keratitis [9]. This particular infection is always extremely difficult to treat, as *Fusarium* spp. is intrinsically

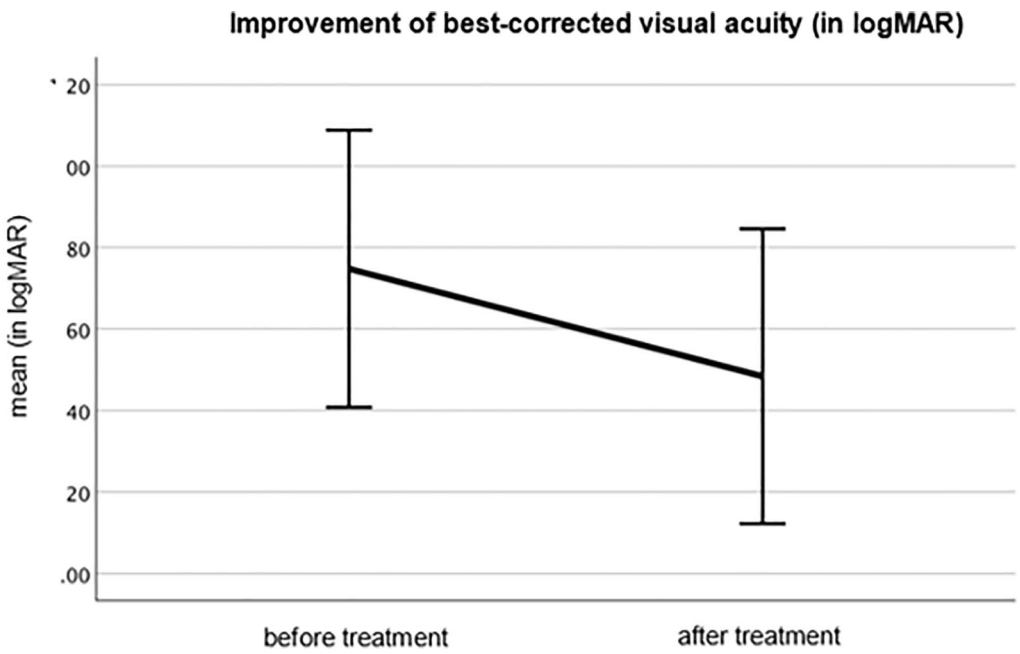

Fig. 5 Mean best-corrected visual acuity (BCVA) improvement comparing visual acuity before and after treatment. Mean BCVA at first presentation was 0.75 logMAR (± 0.82, range 0–2.3 logMAR), with 0.48 logMAR (± 0.88, range − 0.1 to 3) at last presentation. Mean improvement was − 0.26 logMAR (± 1.03). Error bars represent a 95% confidence interval

highly resistant to common antifungals with variable resistance to azole antifungals. Polyene antifungals are the substances with highest susceptibly rates, but of those natamycin is more effective than amphotericin B as a result of its smaller molecular weight. These two factors, the intrinsic resistance of the pathogen itself and the aspect of corneal drug penetration, therefore complicate treatment of *Fusarium* keratitis [3]. Other known risk factors were noted in our study, such as previous ocular surgery, topical and systemic steroid therapy, previous corneal disease and immunosuppression [1, 3, 4, 9, 16]. In eyes without steroid therapy prior to antifungal therapy, the improvement in visual acuity was significantly higher than in eyes with prior anti-inflammatory treatment. In contrast, eyes with prior steroid therapy tended to have better initial visual acuity. Both are presumably due to the immunosuppressive effect.

The increased proportion of female patients, in our case 70%, appears to be attributable to rising contact lens use [3, 9, 17, 18].

The average age of the affected patients in this study was 42 years, similar to two other studies from Germany [3, 4] and two international studies [1, 6] with an expected higher frequency of contact lens use in this age group.

Incidence internationally favours rural regions with 79–84% [18–21]. In our work there was an even split in origin, with 43% of patients living in villages. The risk of injuries with plant-based material could be lower, as there is less agricultural work in Germany than in tropical regions.

The symptoms documented here have been confirmed in other studies: pain, redness, visual loss, photophobia and epiphora [2, 6, 12, 22]. However, fungal keratitis cannot be differentiated from bacterial or viral aetiology on the basis of clinical symptoms [4, 23].

It took an average of 13.88 days from onset of symptoms to correct diagnosis. Other studies stated a significantly longer period of up to 30 days [1, 4, 24]. The average duration from symptom onset to presentation was 6.92 days. Other comparable studies found similar results

with an average of 5–10 days [2, 9, 18, 22, 25, 26].

In our study, the average time from initial presentation to correct diagnosis was 6.96 days, which is significantly lower than in other publications, which may have contributed to better outcomes and a lower rate of surgical interventions [22, 27]. Several studies show that late diagnosis generally leads to a poorer functional outcome [2, 9, 19]. Final BCVA was significantly worse the longer the time from initial presentation or symptom onset to diagnosis. The improvement in BCVA was also significantly lower the longer it took to reach a diagnosis.

In the present study, the pathogen was detected in 44% of cases from contact lens material, in 36% from a corneal scraping and in 20% from a swab. Diagnosis using a conjunctival or a superficial corneal swab is less effective than scraping [12]. In comparable studies, pathogens were detected from swabs in around 60% of cases. Detection from contact lens material often proved to be contamination [1, 3, 4, 28].

IVCM generally provides a fast and non-invasive method for diagnosis. However, Hau and colleagues showed in a study published in 2010 that the diagnostic precision depends on the experience of the observer [14]. With little experience, there may be possible confusion between hyphae and other structures such as artifacts or corneal nerve fibres [28]. Corneal nerves in the stroma, at 25–50 µm, are thicker than hyphae (3–5 µm) [29]. Filamentous fungi have characteristic linear branches that are arranged at angles of 45° (*Aspergillus*) or 90° (*Fusarium*), allowing a skilled examiner to perform a more precise pathogen determination [14]. IVCM was rarely performed (16%) in our clinic because of limited availability of contact microscopy and general unsuitability (reduced compliance due to pain, blepharospasm, small infiltrate size).

In our cases, there was no significant difference in BCVA improvement regarding the localization of infiltrates, while other studies demonstrated a statistically significant association between central localization and reduced final BCVA [30].

The most common topical treatment in our institution was a combination of voriconazole 2% and natamycin 5%, in keeping with current recommendations [26, 31]. Both of these are not commercially available in Germany. The pharmacy at the university hospital rechts der Isar was able to establish regular imports of 5% natamycin after several years. A concentration of 2% voriconazole eye drops is frequently recommended as it provides good results without additional complications or side effects [24]. Voriconazole 400 mg orally once daily was used in 56% of cases. Although a combined treatment of systemic and topical application of voriconazole did not show any benefit over local therapy alone in the Mycotic Ulcer Treatment Trial II (MUTT II), a secondary analysis found that eyes with *Fusarium* infection seemed to benefit from it [32, 33]. It should be prescribed primarily in severe cases or intraocular involvement.

As a result of its low molecular weight of 349.32 Da voriconazole shows good corneal drug penetration, while natamycin with 665.75 Da and even amphotericin B with 924.10 Da have difficulty penetrating the corneal epithelium [4, 31]. For this reason, some studies recommend regular corneal abrasions [24]. Owing to its good tissue penetration, systemic application of voriconazole is useful in cases of intraocular involvement. During treatment regular blood work regarding liver and kidney function is recommended [24].

The use of topical steroids in the treatment of fungal keratitis is controversial. Uncontrolled administration of steroids can lead to devastating outcomes. Steroid therapy should be initiated with one to two drops per day after an intensive antifungal treatment with close monitoring using a slit lamp [34, 35]. Behrens-Baumann reported good results when initiating topical steroid therapy 9 days after infection [10], reflected in our average of 8.62 days.

Various studies report a duration of treatment from 18 to 41.5 days [26, 36]. The average treatment duration in this study was 75.40 days. Outcomes were good, with improved BCVA in 68% of eyes and stable BCVA in 16%. Unfortunately, as a result of the small sample size and subgroups, a statistical analysis regarding management was not possible. Generally, studies show poor outcomes in cases of fungal keratitis, but a few studies have

found an improvement in BCVA [1, 4, 37]. Poor initial BCVA has been noted as a predictor for negative functional outcomes [37]. Our data also demonstrated that a poor initial BCVA significantly prolonged the duration of treatment.

While some authors recommend early pKP to reduce pathogen load, others discuss the challenges of surgery in emergency situations. There is a significantly increased risk of rejection and graft failure [12, 38]. In our collective, 16% of eyes underwent pKP. This is low in national comparison. One study reported a rate of 45%, including enucleations [3], while others reported a rate of 70% [22]. In this study, a significantly lower improvement in BCVA was observed in eyes that underwent pKP compared to eyes that did not require pKP. Various international studies have also shown that pKP under non-ideal conditions is associated with poorer visual outcome [1, 4, 18, 39].

As a surgical alternative, an amniotic membrane transplantation can be performed in selected cases. This was performed in 16% of the eyes in this study. Amnion transplantation promotes wound healing through its anti-inflammatory properties and can sometimes prevent corneal melting [40–42].

The frequency of enucleation has been reported to be 5–9% in other studies [1, 4, 43]. Fortunately, no enucleation was necessary in this study. Possible reasons for this could be the rapid diagnosis and intensive treatment with combination therapy.

Limitations of our study include the following: it was performed in a retrospective fashion and the sample size was relatively small, due to the rare nature of the disease. As a result of the small sample size, a statistically significant comparison between different treatment types or combinations thereof was not possible. Larger case numbers are needed to examine this further.

A consistent application of a combined treatment of natamycin 5% and voriconazole 2% has only been established at the university hospital rechts der Isar since 2016; other different combinations of treatments were due to pre-treatment or adjustments in reference to antifungal resistance.

Furthermore some patients may have been overlooked because of the retrospective nature of the study. Our study tried to avoid contaminations by only including eyes with cultural findings of filamentous fungi showing clinical signs of keratitis, which were treated with antifungal medication.

CONCLUSION

The increase in contact lens-associated infections should prompt the treating physician to consider fungal or at least mixed infections when antibiotics fail. Rapid diagnosis and correct initiation of treatment are important for functional and morphological outcomes. Easier access to natamycin 5% in Germany, without relying on orders and delivery times from a foreign pharmacy, is imperative. Further studies are needed for continuous improvement of treatment regimens. Reporting cases of fungal keratitis to the German fungal keratitis registry is important for obtaining further data on pathogens, epidemiology, and resistance.

ACKNOWLEDGEMENTS

We thank the participants of the study.

Author Contributions. All authors contributed to the study conception and design. Daniel Zapp and Kathrin Rothe conceived the original idea. Material preparation and data collection were performed by Julia Storr. Statistical analysis was performed by Nathalie Bleidißel. The first draft of the manuscript was written by Julia Storr. Daniel Zapp, Nathalie Bleidißel, Christian S. Mayer, Mathias M. Maier and Kathrin Rothe commented on previous versions of the manuscript. Supervision was performed by Kathrin Rothe. All authors read and approved the final manuscript.

Funding. Open Access funding enabled and organized by Projekt DEAL. The authors did not receive support from any organization for the submitted work. The journal's Rapid Service Fee was funded by Technical University of Munich.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. The authors (Julia Storr, Daniel Zapp, Nathalie Bleidißel, Christian S. Mayer, Mathias M. Maier, Kathrin Rothe) declare they have nothing to disclose.

Ethical Approval. This research study was conducted retrospectively from data obtained for clinical purposes. Approval was obtained from the ethics committee of Technical University of Munich (738/20 S-EB). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. This type of study does not require informed consent.

REFERENCES

1. Nielsen SE, Nielsen E, Julian HO, et al. Incidence and clinical characteristics of fungal keratitis in a Danish population from 2000 to 2013. Acta Ophthalmol. 2015;93(1):54–8.
2. Brown L, Leck AK, Gichangi M, Burton MJ, Denning DW. The global incidence and diagnosis of fungal keratitis. Lancet Infect Dis. 2021;21(3):e49–57.
3. Walther G, Stasch S, Kaerger K, et al. Fusarium keratitis in Germany. J Clin Microbiol. 2017;55(10):2983–95.
4. Roth M, Daas L, Renner-Wilde A, et al. The German keratomycosis registry: initial results of a multicenter survey. Ophthalmologe. 2019;116(10):957–66.
5. Cheikhrouhou F, Makni F, Neji S, et al. Epidemiological profile of fungal keratitis in Sfax (Tunisia). J Mycol Med. 2014;24(4):308–12.
6. Hoffman JJ, Burton MJ, Leck A. Mycotic keratitis-a global threat from the filamentous fungi. J Fungi (Basel), 2021;7(4):273.
7. Bullock JD, Warwar RE, Elder BL, Khamis HJ. Microbiological investigations of ReNu plastic bottles and the 2004 to 2006 ReNu with MoistureLoc-related worldwide fusarium keratitis event. Eye Contact Lens. 2016;42(3):147–52.
8. Durand ML. Bacterial and fungal endophthalmitis. Clin Microbiol Rev. 2017;30(3):597–613.
9. Thomas PA, Kaliamurthy J. Mycotic keratitis: epidemiology, diagnosis and management. Clin Microbiol Infect. 2013;19(3):210–20.
10. Behrens-Baumann W. [Keratomycosis: diagnosis and therapy]. Ophthalmologe. 2009;106(5):471–80; quiz 481.
11. Thomas PA, Leck AK, Myatt M. Characteristic clinical features as an aid to the diagnosis of suppurative keratitis caused by filamentous fungi. Br J Ophthalmol. 2005;89(12):1554–8.
12. Winiarczyk M, Borkowska A, Mackiewicz J. Fusarium keratitis as a growing problem—case report and literature review. Ann Agric Environ Med. 2021;28(3):409–13.
13. Zhivov A, Stachs O, Stave J, Guthoff RF. In vivo three-dimensional confocal laser scanning microscopy of corneal surface and epithelium. Br J Ophthalmol. 2009;93(5):667–72.
14. Hau SC, Dart JK, Vesaluoma M, et al. Diagnostic accuracy of microbial keratitis with in vivo scanning laser confocal microscopy. Br J Ophthalmol. 2010;94(8):982–7.
15. Manikandan P, Abdel-Hadi A, Randhir Babu Singh Y, et al. Fungal keratitis: epidemiology, rapid detection, and antifungal susceptibilities of fusarium

and aspergillus isolates from corneal scrapings. Biomed Res Int. 2019;2019:6395840.

16. Szaliński M, Zgryźniak A, Rubisz I, Gajdzis M, Kaczmarek R, Przeździecka-Dołyk J. Fusarium keratitis-review of current treatment possibilities. J Clin Med. 2021;10(23):5468.

17. Sharma S, Das S, Virdi A, et al. Re-appraisal of topical 1% voriconazole and 5% natamycin in the treatment of fungal keratitis in a randomised trial. Br J Ophthalmol. 2015;99(9):1190–5.

18. Khurana A, Kumar A, Chauhan L. Clinical profile and treatment outcomes of Fusarium keratitis. Indian J Ophthalmol. 2022;70(3):852–9.

19. Brown L, Kamwiziku G, Oladele RO, et al. The case for fungal keratitis to be accepted as a neglected tropical disease. J Fungi (Basel). 2022;8(10):1047.

20. Bharathi MJ, Ramakrishnan R, Vasu S, Meenakshi R, Palaniappan R. Epidemiological characteristics and laboratory diagnosis of fungal keratitis. A three-year study. Indian J Ophthalmol. 2003;51(4):315–21.

21. Lin Y, Zhang J, Han X, Hu J. A retrospective study of the spectrum of fungal keratitis in southeastern China. Ann Palliat Med. 2021;10(9):9480–7.

22. Kovalchuk B, Khoramnia R, Tóth M, Horner S, Auffarth GU, Augustin VA. Fusarium keratitis-an upcoming threat in Germany? Ophthalmologie. 2022;119(10):1022–34.

23. Dahlgren MA, Lingappan A, Wilhelmus KR. The clinical diagnosis of microbial keratitis. Am J Ophthalmol. 2007;143(6):940–4.

24. Roth M, Steindor F, Kurzai O, Behrens-Baumann W, Mackenzie CR, Geerling, G. Mykotische Keratitis: Klinische Zeichen, Diagnose, Therapie. Augenheilkunde Up2date. 2020;10:8–16.

25. Hoffman JJ, Yadav R, Sanyam SD, et al. Topical chlorhexidine 0.2% versus topical natamycin 5% for the treatment of fungal keratitis in Nepal: a randomized controlled noninferiority trial. Ophthalmology. 2022;129(5):530–541.

26. Prajna NV, Krishnan T, Mascarenhas J, et al. The mycotic ulcer treatment trial: a randomized trial comparing natamycin vs voriconazole. JAMA Ophthalmol. 2013;131(4):422–9.

27. Ansari Z, Miller D, Galor A. Current thoughts in fungal keratitis: diagnosis and treatment. Curr Fungal Infect Rep. 2013;7(3):209–18.

28. Ong HS, Fung SSM, Macleod D, Dart JKG, Tuft SJ, Burton MJ. Altered patterns of fungal keratitis at a london ophthalmic referral hospital: an eight-year retrospective observational study. Am J Ophthalmol. 2016;168:227–36.

29. Labbé A, Khammari C, Dupas B, et al. Contribution of in vivo confocal microscopy to the diagnosis and management of infectious keratitis. Ocul Surf. 2009;7(1):41–52.

30. Sengupta S, Rajan S, Reddy PR, et al. Comparative study on the incidence and outcomes of pigmented versus non pigmented keratomycosis. Indian J Ophthalmol. 2011;59(4):291–6.

31. Behrens-Baumann W, Finis D, MacKenzie C, Roth M, Geerling G. Keratomycosis—therapy standards and new developments. Klin Monbl Augenheilkd. 2015;232(6):754–64.

32. Prajna NV, Krishnan T, Rajaraman R, et al. Effect of oral voriconazole on fungal keratitis in the mycotic ulcer treatment trial II (MUTT II): a randomized clinical trial. JAMA Ophthalmol. 2016;134(12):1365–72.

33. Prajna NV, Krishnan T, Rajaraman R, et al. Adjunctive oral voriconazole treatment of fusarium keratitis: a secondary analysis from the mycotic ulcer treatment trial II. JAMA Ophthalmol. 2017;135(6):520–5.

34. Behrens-Baumann W. Adjunctive corticosteroids for antimicrobial treatment. Ophthalmologe. 2016;113(11):964–5.

35. Schmack I, Müller M, Kohnen T. Microbial keratitis—part 2: specific aspects of mycotic and acanthamoeba keratitis. Klin Monbl Augenheilkd. 2018;235(4):511–30.

36. Sharma N, Sahay P, Maharana PK, et al. Management algorithm for fungal keratitis: the TST (topical, systemic, and targeted therapy) protocol. Cornea. 2019;38(2):141–5.

37. Prajna NV, Krishnan T, Mascarenhas J, et al. Predictors of outcome in fungal keratitis. Eye (Lond). 2012;26(9):1226–31.

38. Maier P, Böhringer D, Reinhard T. Clear graft survival and immune reactions following emergency keratoplasty. Graefes Arch Clin Exp Ophthalmol. 2007;245(3):351–9.

39. Iselin KC, Baenninger PB, Schmittinger-Zirm A, Thiel MA, Kaufmann C. Fungal keratitis: a six-year review at a tertiary referral centre. Klin Monbl Augenheilkd. 2017;234(4):419–25.

40. Kim JS, Kim JC, Hahn TW, Park WC. Amniotic membrane transplantation in infectious corneal ulcer. Cornea. 2001;20(7):720–6.

41. Ma DH, Wang SF, Su WY, Tsai RJ. Amniotic membrane graft for the management of scleral melting and corneal perforation in recalcitrant infectious scleral and corneoscleral ulcers. Cornea. 2002;21(3):275–83.

42. Lin HC, Chu PH, Kuo YH, Shen SC. Clinical experience in managing Fusarium solani keratitis. Int J Clin Pract. 2005;59(5):549–54.

43. Watson SL, Cabrera-Aguas M, Keay L, Khoo P, McCall D, Lahra MM. The clinical and microbiological features and outcomes of fungal keratitis over 9 years in Sydney. Australia Mycoses. 2020;63(1):43–51.