Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Clinical Characteristics and Treatment Outcomes of Pediatric Fungal Keratitis

Jing Zhang[1–3], Huabo Chen[1–3], Vishal Jhanji[4], Bining Zhang[1–3], Lixin Xie[1–3], Yanling Dong[1–3]

[1]Eye Institute of Shandong First Medical University, Qingdao Eye Hospital of Shandong First Medical University, Qingdao, People's Republic of China; [2]State Key Laboratory Cultivation Base, Shandong Provincial Key Laboratory of Ophthalmology, Qingdao, People's Republic of China; [3]School of Ophthalmology, Shandong First Medical University, Qingdao, People's Republic of China; [4]Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Correspondence: Lixin Xie; Yanling Dong, Qingdao Eye Hospital of Shandong First Medical University, 5 Yanerdao Road, Qingdao, Shandong, 266071, People's Republic of China, Email lixin_xie@hotmail.com; yanling1235@126.com

Background: Fungal keratitis is relatively rare in children. This study aimed to analyze the clinical characteristics and treatment outcomes of pediatric fungal keratitis.

Methods: A retrospective review of medical records was conducted for children (aged <18 years) diagnosed with fungal keratitis from 1996 to 2021. Demographic features, etiology, clinical characteristics, and treatment outcomes were collected.

Results: Forty-seven children (48 eyes) were included (31 males, 16 females). The mean age of onset was 11.8±4.1 (range: 1–17) years. The leading cause of fungal keratitis was trauma including dust or ocular foreign body (29.2%) and vegetative matter (25.0%). *Fusarium* (41.7%) and *Aspergillus* (20.8%) were the main causative organisms. 16.7% (8/48) of the infected eyes were treated successfully with medications. Voriconazole had the highest drug sensitivity rate (70.0%). 66.7% (32/48) of the eyes required therapeutic keratoplasty (21 eyes penetrating keratoplasty, 11 eyes lamellar keratoplasty). The diameter of the corneal ulcer was significantly associated with keratoplasty (OR 3.556, $p = 0.014$). The peripheral blood neutrophil/lymphocyte ratio (NLR) showed positive correlation with the age of onset ($r = 0.437$, $p = 0.002$) and the diameter of corneal ulcer ($r = 0.298$, $p = 0.04$). Logistic regression analysis revealed a significant association between NLR and the need for surgical treatment (odds ratio = 117.926, $p = 0.019$).

Conclusion: In the current study, ocular trauma was the leading cause of fungal keratitis in the pediatric age group. *Fusarium* was the most common organism. Voriconazole was the preferred antifungal drug. Surgical treatment was necessary in two-thirds of the eyes.

Keywords: keratitis, fungi, children, treatment, outcomes

Introduction

Fungal keratitis is relatively rare in children.[1] There was only one case (5.9%) with fungal infection in a five-year study of childhood infectious keratitis in Canada.[2] In a 23-year study of childhood infectious keratitis in the United States, 12 cases of fungal infection occurred.[3] Recently, neutrophil-to- lymphocyte ratio (NLR) has been used as a marker for systemic inflammatory status.[4] The NLR is the total count of neutrophils divided by those of lymphocytes. It has been recognized as a valuable marker of systemic inflammation, which is significantly increased in many eye disorders, such as keratoconus, glaucoma, and pterygium.[5,6] NLR in childhood differs from that in adulthood. It shows higher values directly after birth, then gradually decreases, and starts to slowly increase around the age of 3, gradually approaching adult levels.[7] In this study, we retrospectively review the medical records of pediatric patients with fungal keratitis who were treated in our hospital between 1996 and 2021. We also investigated the potential association between NLR and outcomes of fungal keratitis.

Fungal keratitis can lead to severe visual impairment. It accounts for about 20% to 60% of all microbial keratitis cases,[8] but seems to be less common in children.[2,3] Our understanding of the unique characteristics of fungal keratitis in children is limited due to its low incidence. The lack of knowledge can result in delayed, incorrect, or inadequate treatment, with long-lasting and devastating consequences. Childhood blindness is a life-long impairment that imposes

Received: 18 November 2024
Accepted: 8 February 2025
Published: 4 March 2025

significant emotional and financial burdens on families and society. Therefore, it is crucial to prioritize the study of PFK to ensure timely and appropriate interventions.

Methods

Study Design and Population

The medical records of children (<18 years old) who were diagnosed with fungal keratitis from 1996 to 2021 were reviewed. The patient's demographic characteristics, risk factors, disease characteristics, treatment, and outcomes were recorded. An informed consent was obtained from the parents and/or legal guardians. This study was approved by the Ethics Committee of Qingdao Eye Hospital of Shandong First Medical University ([2020]19) and adhered to the tenets of the Declaration of Helsinki.

Diagnostic Criteria for Fungal Keratitis

Corneal scrapings were subjected to 10% KOH mount. Corneal scrapings were also plated on Sabouraud's Dextrose Agar for culture and strain identification. In addition, patient's corneas were examined using confocal microscopy. The diagnosis of fungal keratitis was confirmed by the presence of fungal elements in the KOH preparations or confocal microscopic images, or positive culture results.[1,9]

Ocular Examinations

A detailed clinical history was obtained followed by measurement of visual acuity and intraocular pressure. Slit-lamp examination was performed to note the characteristics of the corneal infiltrate. Clinical photographs were obtained on a slit lamp mounted camera (BX900, Haag-Streit) under cobalt blue light after staining with fluorescein dye. Confocal microscopy was performed by an experienced technician (HRT3, Heidelberg).

Treatment Strategy

Once the diagnosis of fungal keratitis was confirmed, antifungal agents, including topical voriconazole 1%, natamycin 5% or amphotericin B 0.25% were administered hourly. Subsequent adjustments were made based on the drug susceptibility results of each patient. If the drug therapy was not effective after one week, either limited superficial keratectomy (for anterior infiltrates) or keratoplasty (for deep infiltrates) was performed. All patients followed this treatment strategy.

Anti-Fungal Drug Sensitivity Tests and Determination of MIC

Anti-fungal drug sensitivity tests were performed in accordance with National Committee for Clinical Laboratory Standards (NCCLS) standard M38-A guidelines as described in previous studies.[10] The control strain was *Candida parapsilosis* (ATCC22019). In brief, seven kinds of anti-fungal drugs were packaged on the 96 well plates in the antifungal drug sensitivity test kits (Jinzhang Medical and New Technological Institute, Tianjin, China), which include amphotericin B, ketoconazole, miconazole, itraconazole, fluconazole, 5-fluorocytosine, and terbinafine. The strains to be examined were inoculated onto PDA media, cultured for two to seven days, and the inoculums were diluted to $(0.5–5)\times10^4$ CFU/mL. Values of minimum inhibitory concentrations (MIC) were read after 24 to 48 hours of incubation at 27 °C.

Statistical Analysis

All data were processed using SPSS 22.0 software. A Chi-squared test was used to compare the incidence at different times and the positive rate of different tests. A comparison of visual acuity between the groups was performed with a Mann–Whitney test. Spearman correlation analysis was used to assess the correlation between the two sets of data. Factors associated with the surgical treatment were assessed using logistic regression analysis. The difference was statistically significant at $p < 0.05$.

Results

Epidemiological Characteristics

A total of 47 children (48 eyes) received treatment for fungal keratitis, representing 16.3% (48/294) of all children with infectious keratitis. Among them, 24.1% (35/145) were reported between 1996 and 2008, and 8.7% (13/149) between 2009 and 2021 ($p = 0.001$, X^2-test). During the same period, 3223 adult patients (3225 eyes) were diagnosed with fungal keratitis, accounting for 59.3% (3225/5435) of all adult patients with infectious keratitis. The incidence of fungal keratitis was significantly lower in children compared to adults ($p < 0.001$, X^2-test).

Out of the 47 enrolled patients, 31 were male (66.0%) and 16 were female (34.0%). The mean age at onset was 11.8 ±4.1 years (range: 1–17 years). Among them, children aged ≤5 years constituted 6.4% (3/47), those aged 6–12 years accounted for 38.3% (18/47), and those aged 13–17 years accounted for 55.3% (26/47). A total of 93.6% (44/47) of patients were from rural areas. No children with a history of diabetes were identified.

70.2% (33/47) of patients were diagnosed between April and September (spring and summer). Additionally, 51.1% (24/47) of the patients visited the hospital within one week of symptoms onset, and only one patient (2.2%) with contact lens-induced fungal keratitis had symptoms lasting for more than one month.

The leading cause of fungal keratitis in children was trauma due to dust or foreign body in the eye (29.2%, 14/48), or trauma with vegetative matter (25.0%, 12/48). There was one case where a 17-year-old boy developed fungal infection after undergoing LASIK surgery for myopia (Table 1). Unexplained fungal keratitis accounted for 25.0% (12/48) of the cases.

A total of 91.7% eyes (44/48) received initial treatment at a local hospital. Of these, 22/44 (50.0%) received a correct diagnosis and received topical antifungals treatment. 27.3% (12/44) of the eyes were treated as bacterial keratitis and 2.3% (1/44) were treated for viral keratitis. Additionally, 20.5% (9/44) of eyes remained undiagnosed or had unclear history about prior topical medication history. 11.4% (5/44) eyes had a definitive history of topical corticosteroid use.

Clinical Features

During the initial visit to the hospital, 31.3% (15/48) of the eyes had a hypopyon, 6.3% (3/48) had corneal perforation, and 6.3% (3/48) had endophthalmitis. The average diameter of the corneal ulcer at the initial visit to our hospital was 4.7 ±2.7 mm (range: 1.5–12.0 mm). 25.0% (12/48) of the eyes had small ulcers (diameter < 3 mm), while 41.7% (20/48) had large ulcers (diameter > 5 mm). The average NLR value was 2.3±1.1 (range: 0.7 to 7.0). NLR was found to be positively correlated with the age of onset ($r = 0.437$, $p = 0.002$) and the diameter of the corneal ulcer ($r = 0.298$, $p = 0.04$).

Table 1 Risk Factors for Fungal Keratitis in Children at the Shandong Eye Institute, 1996–2021

Risk Factors	No. of Eyes	%
Trauma		
Dust, soil, or stone	14	29.2%
Plants/agriculture	12	25.0%
Small winged insect	2	4.2%
Glass	1	2.1%
Firecracker	1	2.1%
Others		
Post-Lasik	2	4.2%
Contact lens	1	2.1%
After respiratory tract infection	3	6.3%
Uncertain	12	25.0%
Total	48	100%

https://doi.org/10.2147/IDR.S507178

Microbiology Results

Fungal smear results were positive in 81.3% (39/48) of cases, whereas fungal culture was positive in 79.2% (38/48) of cases. Confocal microscopy showed a positive result in 85.7% (18/21) of the examined cases. There was no statistical difference among these detection methods ($p = 0.815$, X^2-test). In 62.5% (30/48) infected eyes, the fungal organism was identified. Among these identified fungi, *Fusarium* infection was found in 41.7% (20/48) of cases while *Aspergillus* was responsible for 20.8% (10/48) of cases. In 37.5% (18/48) of cases, the causative agent remained uncertain. Four patients had bacterial co-infections with *Staphylococcus epidermidis, Bacillus subtilis, Enterococcus*, and *Hafnia* (Table 2). There was no significant difference in the clinical features of corneal infections between *Fusarium* and *Aspergillus* (Table 3).

Drug Susceptibility

The mean MIC for *Fusarium* was 1.231 for voriconazole and 1.932 for amphotericin B. In contrast, the mean MIC for itraconazole against *Aspergillus* was the lowest (0.250), followed by voriconazole (0.380) (Table 4).

Table 2 Fungal Spectrum of Pediatric Fungal Keratitis at the Shandong Eye Institute, 1996–2021

	No. of Eyes	%
Fusarium species	20	41.7%
F. moniliforme	8	16.7%
F. solani	4	8.3%
Unknown	8	16.7%
Aspergillus species	10	20.8%
A. fumigatus	7	14.6%
Unknown	3	6.3%
Uncertain	18	37.5%

Table 3 Comparison of Clinical Features Between Fusarium and Aspergillus Keratitis at the Shandong Eye Institute, 1996–2021

	Fusarium Species n=20	Aspergillus Species n=10	p
Mean age of onset (years)	12.4±3.5	10.1±5.0	0.159*
Duration from onset to our hospital visit (days)	16.5±14.4	14.1±9.3	0.747*
Diameter of corneal ulcer (mm)	5.3±2.2	3.8±1.9	0.099*
Neutrophil-to-lymphocyte ratio	2.8±1.7	1.8±0.7	0.125*
Anterior chamber empyema (n)	8	2	0.074#
Endophthalmitis (n)	0	1	0.149#

Notes: *Comparing between two species. P value calculated with *t* test. #Comparing between two species. P value calculated with a Chi-squared test.

Table 4 Pediatric Fungal Keratitis and Commonly Used Antifungal Drugs at the Shandong Eye Institute, 1996–2021 (Minimum Inhibitory Concentrations, g/Ml)

	Fusarium Species n=20		Aspergillus Species n=10		Total n=30	
	MIC	GM	MIC	GM	MIC	GM
Amphotericin B	0.25–16	1.932	0.25–8	2.144	0.25–16	2.000
Ketoconazole	0.5–16	7.464	0.125–16	0.926	0.125–16	3.910
Itraconazole	0.25–32	2.071	0.125–8	0.250	0.125–32	1.0234
Fluconazole	4–64	34.297	16–256	48.503	4–256	38.497
Voriconazole	0.25–16	1.231	0.064–8	0.380	0.125–16	0.832
Natamycin	1–16	2.378	8	8	1–16	3.466
Terbinafine	1–8	2.828	0.5–1	0.926	0.5–8	2

Based on the results of the drug susceptibility tests, the sensitivity of several antifungal drugs against *Fusarium* and *Aspergillus* was evaluated. Voriconazole exhibited the highest sensitivity against *Fusarium*, with a rate of up to 65%, followed by Natamycin and amphotericin B with a sensitivity of 50%. Fluconazole, ketoconazole, and terbinafine showed higher rates of resistance against *Fusarium*, with resistances of 85%, 75%, and 75%, respectively.

For *Aspergillus*, voriconazole demonstrated the highest sensitivity, with a rate of up to 80.0%. Ketoconazole and itraconazole exhibited sensitivities of 70.0%, respectively. In contrast, natamycin exhibited complete resistance (90%) to *Aspergillus*, while amphotericin B and fluconazole showed resistance of 70%. The summarized drug susceptibility results can be found in Table 5.

Table 5 Results of Susceptibility in Children With Fungal Keratitis at the Shandong Eye Institute, 1996–2021

	Fusarium Species n=20	Aspergillus Species n=10	Total n=30
Amphotericin B			
S	10 (50%)	3 (30%)	13 (43.3%)
SDD	0 (0%)	0 (0%)	0 (0%)
I	3 (15%)	0 (0%)	3 (10%)
R	7 (35%)	7 (70%)	14 (46.7%)
Ketoconazole			
S	5 (25%)	7 (70%)	12 (40%)
SDD	0 (0%)	0 (0%)	0 (0%)
I	0 (0%)	1 (10%)	1 (3.3%)
R	15 (75%)	2 (20%)	17 (56.7%)
Itraconazole			
S	3 (15%)	7 (70%)	10 (33.3%)
SDD	5 (25%)	2 (20%)	7 (23.3%)
I	0 (0%)	0 (0%)	0 (0%)
R	12 (60%)	1 (10%)	13 (43.3%)
Fluconazole			
S	3 (15%)	0 (0%)	3 (10%)
SDD	0 (0%)	3 (30%)	3 (10%)
I	0 (0%)	0 (0%)	0 (0%)
R	17 (85%)	7 (70%)	24 (80%)
Voriconazole			
S	13 (65%)	8 (80%)	21 (70%)
SDD	0 (0%)	0 (0%)	0 (0%)
I	2 (10%)	0 (0%)	2 (6.9%)
R	5 (25%)	2 (20%)	7 (24.1%)
Natamycin			
S	10 (50%)	0 (0%)	10 (33.3%)
SDD	5 (25%)	0 (0%)	5 (16.7%)
I	5 (25%)	1 (10%)	6 (20%)
R	0 (0%)	9 (90%)	9 (30%)
Terbinafine			
S	0 (0%)	1 (10%)	1 (3.3%)
SDD	5 (25%)	8 (80%)	13 (43.3%)
I	0 (0%)	1 (10%)	1 (3.3%)
R	15 (75%)	0 (0%)	15 (50%)

Abbreviations: S, susceptible; SDD, susceptible-dose dependent; I, intermediary; R, resistant.

https://doi.org/10.2147/IDR.S507178

Treatment and Outcomes

Overall, only 16.7% (8/48) were successfully treated with medical management alone. Seven eyes (14.6%) underwent superficial keratectomy due to worsening of the disease (increase in corneal ulcer area or deepening of infiltration) during medical treatment and were subsequently cured. 66.7% (32/48) of the eyes required keratoplasty, with 21 eyes receiving PKP and 11 eyes receiving LKP. Enucleation was required in one eye (2.1%). Logistic regression analysis revealed a significant association between NLR and the need for surgical treatment (odds ratio = 117.926, $p = 0.019$) (Table 6). Additionally, the diameter of the corneal ulcer was found to be significantly associated with the need for keratoplasty (odds ratio = 3.556, $p = 0.014$) (Table 7).

In the *Fusarium* group, 45% (9/20) of the cases had LKP, 40% (8/20) had PKP, 10% (2/20) had excision of lesion, and 5% (1/20) were treated with topical medications alone. In the *Aspergillus* group, 20% (2/10) had LKP, 70% (7/10) had PKP, and 10% (1/10) had superficial keratectomy.

The recurrence rate of keratitis after keratoplasty was 3.1% (1/32) during the follow-up period of 4.0 ± 3.9 (0.6–13.9) years. In one patient with *Aspergillus* infection, the infiltration recurred three days after LKP (9.1%, 1/11), and a PKP was required. During a follow-up period of 3.8 ± 4.1 (1.2–13.9) years, there were three instances of graft rejection (14.3%) after PKP, between 1 and 23 months after the surgery. However, all cases responded well to topical treatment with corticosteroids.

The median best corrected visual acuity (BCVA) after PKP was 20/50 (20/200 – 20/25), with 42% of the eyes achieving a BCVA of ≥20/40. After LKP, the median BCVA was 20/50 (20/100 – 20/40), with 36.4% of the eyes achieving a BCVA ≥ 20/40. The median BCVA after medical treatment was 20/50 (20/400 – 20/20), 26.7% of the eyes

Table 6 Results of the Regression Analysis of the Various Risk Factors for Surgical Treatment for Pediatric Fungal Keratitis

Risk Factor	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Sex (male)	5.10	0.093–2.799	0.510			
Age	1.374	1.099–1.719	0.005*	1.261	0.838–1.898	0.266
Onset of illness ≥7 days	0.15	0.031–0.723	0.018*	0.072	0.003–1.764	0.107
Topical steroid use	0		0.999			
Diameter of corneal ulcer	2.177	1.130–4.192	0.02*	3.070	0.770–12.237	0.112
Neutrophil/lymphocyte ratio	13.562	2.022–90.962	0.007*	117.926	2.172–6403.311	0.019*
Anterior chamber empyema	−6.202	−20.552–0.247	0.093			
Corneal perforation	0		0.999			
Endophthalmitis	0		0.999			

Note: *P value calculated with logistic regression analysis.

Table 7 Results of the Regression Analysis of the Various Risk Factors for Keratoplasty for Pediatric Fungal Keratitis

Risk Factor	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Sex (male)	0.636	0.166–2.446	0.511			
Age	1.223	1.036–1.444	0.017*	1.146	0.904–1.455	0.260
Onset of illness ≥7 days	0.089	0.021–0.375	0.001*	0.306	0.051–1.850	0.306
Topical steroid use	3.333	0.472–23.535	0.227			
Diameter of corneal ulcer	3.607	1.573–8.270	0.002*	3.556	1.293–9.776	0.014*
Neutrophil/lymphocyte ratio	2.587	0.934–7.164	0.067			
Anterior chamber empyema	0.237	0.046–1.225	0.086			
Corneal perforation	0		0.999			
Endophthalmitis	1.107	0.093–13.248	0.936			

Note: *P value calculated with logistic regression analysis.

achieved ≥20/40. There was no significant difference between BCVA between PKP and LKP eyes (p = 0.913). Additionally, no statistically significant difference was found between BCVA after medical treatment and corneal transplantation (p = 0.951). However, the BCVA after treatment was lower in children ≤8 years [median 20/60 (20/400 – 20/40)] compared to children >8 years [median; 20/50 (20/200 – 20/20); p = 0.032].

Discussion

This study represents the largest investigation to date focusing on pediatric fungal keratitis. Fungal keratitis is the predominant cause of infectious corneal ulcers in Northern China, mainly related to injuries with vegetative matter.[1] In this study, most of the participants were from rural areas, where the risk of injury is higher compared to urban regions. It is noteworthy that over the last 12 years, the incidence of fungal keratitis in children has dropped to 8.7%, which is comparable to that in the United States.[3]

Medical management of fungal keratitis involves the use of antifungal drugs including polyenes (amphotericin B, natamycin, and nystatin), azoles (ketoconazole, miconazole, econazole, fluconazole, itraconazole, voriconazole, and posaconazole), allylamine (terbinafine) and echinocandins (caspofungin). Suboptimal corneal penetration of these drugs is a major limitation. The newer triazoles such as voriconazole have exhibited excellent corneal penetration even through an intact corneal epithelium. Voriconazole is potent against a wide spectrum of fungi, such as *C. albicans, C. parapsilosis, C. tropicalis, A. fumigatus, A. flavus, and F. solani*. In our study, voriconazole was the most effective antifungal drug with the most favorable MIC values (Table 5). Early administration of the correct medication is particularly crucial for fungal keratitis. Incorrect topical steroid use can rapidly worsen the condition.

Corneal transplantation in children is associated with a higher incidence of complications compared to adult surgery.[11] However, in this study, where the average age of the patients was 12 years old, the incidence of postoperative complications was not significantly different from that observed in adults.[12–14] The growth patterns of *Fusarium* and *Aspergillus* are different in the cornea, with about 90% of *Fusarium hyphae* aligning parallel to the corneal stromal lamellae, while *Aspergillus* exhibits more vertical growth.[15] To mitigate rejection and the long-term complications such as corneal endothelial failure, LKP is recommended for corneal ulcers caused by *Fusarium* injection.[9] However, the oblique growth pattern of *Aspergillus* contributes to its greater erosive potential and the subsequent need for PKP.[10,13] Monocular vision abnormalities in childhood can lead to amblyopia, which explains the lower BCVA observed in children aged ≤8 years compared to older children.

The etiology, onset time and seasonal characteristics of pediatric fungal corneal ulcers are similar to those in adults. Fungal corneal ulcers occurring in children do not exhibit greater severity than those in adults, despite their immature immune defenses. In addition, a low NLR in children may serve as a protective factor against fungal corneal ulcers. In certain cases, an excessive activation of immune cells leads to the release of large quantities of cytokines, resulting in an uncontrollable cascade or a cytokine storm. This severe immune response can cause significant damage to human tissues and organs.[16,17] In fungal corneal ulcers, neutrophils can play a dual role by both combating fungal pathogens and causing corneal damage through the release of reactive oxygen species (ROS) and proteases.[18–20] In this study, the association of a higher NLR in the peripheral blood with a larger corneal ulcer diameter, supports the dual role theory. Currently, there are a limited number of studies on lymphocytes and infectious eye diseases, highlighting the need for further investigations in this area.

In summary, our study identified that the incidence of fungal keratitis is lower in children compared to adults. A low NLR in childhood might serve as a protective factor against severe ulcers. Corneal transplantation remains a viable option to provide the long-term improvement in BCVA.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, Yl Dong, upon reasonable request.

Acknowledgment

Funding information is not available.

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Xie L, Zhong W, Shi W, Sun S. Spectrum of fungal keratitis in north China. *Ophthalmology*. 2006;113:1943–1948. doi:10.1016/j.ophtha.2006.05.035
2. Noureddin GS, Sasaki S, Butler AL, et al. Paediatric infectious keratitis at tertiary referral centres in Vancouver, Canada. *Br j Ophthalmol*. 2016;100:1714–1718. doi:10.1136/bjophthalmol-2015-308034
3. Rossetto JD, Cavuoto KM, Osigian CJ, et al. Paediatric infectious keratitis: a case series of 107 children presenting to a tertiary referral centre. *Br j Ophthalmol*. 2017;101:1488–1492. doi:10.1136/bjophthalmol-2016-310119
4. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med*. 2012;5(1):2. doi:10.1186/1755-7682-5-2
5. Shirvani M, Soufi F, Nouralishahi A, et al. The diagnostic value of neutrophil to lymphocyte ratio as an effective biomarker for eye disorders: a meta-analysis. *Biomed Res Int*. 2022;2022:5744008. doi:10.1155/2022/5744008
6. Reyhan AH, Karadağ AS, Şş Ç. Assessing the role of systemic inflammation in the etiopathogenesis of advanced stage keratoconus. *Indian J Ophthalmol*. 2021;69(10):2658–2662. doi:10.4103/ijo.IJO_3403_20
7. Moosmann J, Krusemark A, Dittrich S, et al. Age- and sex-specific pediatric reference intervals for neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and platelet-to-lymphocyte ratio. *Int J Lab Hematol*. 2022;44(2):296–301. doi:10.1111/ijlh.13768
8. 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–e57. doi:10.1016/S1473-3099(20)30448-5
9. Xie L, Hu J, Shi W. Treatment failure after lamellar keratoplasty for fungal keratitis. *Ophthalmology*. 2008;115:33–36. doi:10.1016/j.ophtha.2007.03.072
10. Xie L, Zhai H, Zhao J, Sun S, Shi W, Dong X. Antifungal susceptibility for common pathogens of fungal keratitis in Shandong Province, China. *Am J Ophthalmol*. 2008;146(2):260–265. doi:10.1016/j.ajo.2008.04.019
11. Vanathi M, Raj N, Kusumesh R, Aron N, Gupta N, Tandon R. Update on pediatric corneal diseases and keratoplasty. *Surv Ophthalmol*. 2022;67(6):1647–1684. doi:10.1016/j.survophthal.2022.07.010
12. Aruljyothi L, Radhakrishnan N, Prajna VN, Lalitha P. Clinical and microbiological study of paediatric infectious keratitis in South India: a 3-year study (2011-2013). *Br j Ophthalmol*. 2016;100:1719–1723. doi:10.1136/bjophthalmol-2015-307631
13. Xie L, Shi W, Liu Z, Li S. Lamellar keratoplasty for the treatment of fungal keratitis. *Cornea*. 2002;21:33–37. doi:10.1097/00003226-200201000-00008
14. Xie L, Dong X, Shi W. Treatment of fungal keratitis by penetrating keratoplasty. *Br j Ophthalmol*. 2001;85:1070–1074. doi:10.1136/bjo.85.9.1070
15. Xie L, Zhai H, Shi W, Zhao J, Sun S, Zang X. Hyphal growth patterns and recurrence of fungal keratitis after lamellar keratoplasty. *Ophthalmology*. 2008;115(6):983–987. doi:10.1016/j.ophtha.2007.07.034
16. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5
17. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507–513. doi:10.1016/S0140-6736(20)30211-7
18. Jin X, Zhao Y, Zhang F, et al. Neutrophil extracellular traps involvement in corneal fungal infection. *Mol Vis*. 2016;22:944–952.
19. Zhai HL, Xie LX, Dong XG. The roles of gelatinases in pathological changes of fungal keratitis in experimental rabbits. *Zhonghua Yan Ke Za Zhi*. 2007;43(9):817–822.
20. Ahn CM, Sandler H, Saldeen T. Decreased lung hyaluronan in a model of ARDS in the rat: effect of an inhibitor of leukocyte elastase. *Ups J Med Sci*. 2012;117(1):1–9. doi:10.3109/03009734.2011.622812