Original Article

A study on childhood microbial keratitis in South India

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Purpose: The aim of this study was to determine the predisposing risk factors, clinical characteristics, microbiological profile, and visual and functional treatment outcome of microbial keratitis including viral keratitis in children. **Methods:** A prospective study was carried out in a tertiary care institute over a period of 18 months on 73 pediatric patients. Data collected was analyzed for demographics of the patient population, causative organisms, and management outcome in terms of visual and functional outcome. **Results:** Patients in the age group from 1 month to 16 years were included, with a mean age of 10.81 years. Trauma was the commonest risk factor (40.9%), with unidentified foreign body fall being the most common (32.3%). No predisposing factors were identified in 50% of cases. Also, 36.8% of eyes were culture positive, with bacterial isolates in 17.9% and fungus in 82.1%. Moreover, 7.1% eyes were culture positive for *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* each. *Fusarium* species (67.8%) was the commonest fungal pathogen, followed by *Aspergillus* species (10.7%). Also, 11.8% were clinically diagnosed as viral keratitis. No growth was found in 63.2% of patients. Treatment with broad-spectrum antibiotics/antifungals was administered in all cases. At the final follow-up, 87.8% achieved a best corrected visual acuity (BCVA) of 6/12 or better. Therapeutic penetrating keratoplasty (TPK) was required by 2.6% of eyes. **Conclusion:** Trauma was the major cause for pediatric keratitis. Majority of the eyes responded well to medical treatment, with only two eyes needing TPK. Early diagnosis and prompt management helped majority of the eyes to achieve a good visual acuity after the resolution of keratitis.

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Microbial keratitis is an infectious disease of the cornea, characterized by inflammation, usually with stromal infiltration by leukocytes. Visual outcomes including permanent visual dysfunction have been reported in a number of patients in both developed and developing countries.[1]

Although the incidence of pediatric keratitis is low among cases of microbial keratitis,[2] it is concerning due to the risk of development of amblyopia in this age group. The challenges associated with pediatric keratitis are difficulty in clinical examination, higher level of inflammation in children in comparison to adults, and difficulty in administering topical medications.[3] Early diagnosis, intensive drug treatment, and timely planned surgical intervention may effectively improve the outcome of pediatric microbial keratitis.

The microbiological profile in keratitis shows huge disparities among developed[4,5] and developing countries.[6] The risk factors predisposing for microbial keratitis also vary with the geographic location.

In this context, studies pertaining to a particular geographic area regarding the risk factors, demographic pattern, most common causative organisms, antimicrobials that they are susceptible to, clinical features, and visual outcomes are of utmost importance, in order to develop a comprehensive strategy for treatment and prevention of corneal infections.

Methods

This was a prospective study carried out in the outpatient department (OPD) of the cornea clinic and the pediatric ophthalmology clinic at a tertiary care center in South India over a study duration of 18 months. The requisite clearance for the study was obtained from the Institutional Ethics Committee. An informed consent for participation in the study was obtained from all patients/parents. The inclusion criteria for the study were presence of corneal epithelial defect and stromal infiltration on slit-lamp examination and microbiological investigations for corneal ulcer. All cases with smear-positive or smear-negative, culture-positive or culture-negative reports were included if the clinical picture was consistent with microbial keratitis. Noncompliant patients were excluded.

All patients underwent comprehensive examination with a thorough history taking. Examination of visual acuity (with Snellen's chart in verbal children and fixation and other charts in pre-verbal children) and slit-lamp biomicroscopy for determination of the dimensions and location of corneal ulcer

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were carried out. All eyes were subjected to microbiological examination, which included two scrapings for smear examination (one each for gram's stain and potassium hydroxide wet mount) and subsequent scrapings for culture plating (on blood agar, potato dextrose agar, or non-nutrient agar). Corneal scrapings were obtained under topical anesthesia or under sedation, as required. Antibiotic sensitivity was done for all bacterial corneal ulcers.

Initial treatment was started on the basis of clinical evaluation and microbiological smear examination. Eyes with positive fungal smears were treated with 5% natamycin suspension, and 1% voriconazole was added in large/ deep ulcers not responding to treatment. Eyes positive for gram-positive organisms were treated with 0.5% moxifloxacin eye drops, and eyes positive for gram-negative organisms were treated with amikacin 0.3% and moxifloxacin eye drops. In suspected viral ulcers, samples were sent for viral polymerase chain reaction (PCR) and patients were started on topical acyclovir. Smear-negative patients were initially treated empirically, based on clinical characteristics. In cases with ambiguous presentation, patients were treated with both 5% natamycin and 0.5% moxifloxacin concurrently. The treatment was modified based on culture and sensitivity reports. Culture was considered positive when it was consistent with clinical signs and the same organism was grown in more than one media. In cases of perforation, progressive ulcer (reaching near limbus), and cases not responding to medical treatment, therapeutic penetrating keratoplasty (TPK) was done.

Results

Categorical data was compared by Fisher's exact test/ Chi-squared test. Mean difference between pre- treatment and post-treatment of the ocular parameters was compared by paired t-test/ Wilcoxon signed rank test. All the statistical analyses were performed by STATA 11.1 (Stata Corp, Texas, USA). *P* value less than 0.05 was considered as statistically significant.

This study involved 76 eyes of 73 patients, in the age group from 1 month to 16 years, with a mean age of 10.81 years. Thirty-seven patients (50.7%) were between 11 and 16 years of age. Forty-four (60.3%) were males and 29 (39.7%) were females, with a male to female ratio of 1.5:1. Also, 53 (72.6%) of them were from urban areas, while 20 (27.4%) were from rural areas.

The right eye was involved in 34 cases and the left eye in 36 cases, while three patients had bilateral involvement. The most common presenting complaint was redness (98.6%), followed by pain in eye (89%). The mean duration from the onset of symptoms to the time of presentation was 4.19 days, with 78.1% (57) patients presenting within the first week.

Fig. 1 shows data of the predisposing factors leading to microbial keratitis. Thirty-one eyes (40.9%) had previous history of trauma/injury, of which fingernail injury was seen in seven eyes (22.6%), stick injury in five (16.1%) eyes, injury with stones in three eyes (9.7%), and unidentified foreign body fall was seen in 10 eyes (32.3%). In 38 eyes (50%), no predisposing factors were identified. The likely explanation for this is probably an incorrect history due to misinformation given by the child. There may be a reluctance on the part of the child to inform the parents regarding any trauma sustained while playing, due to the fear of punishment or scolding.

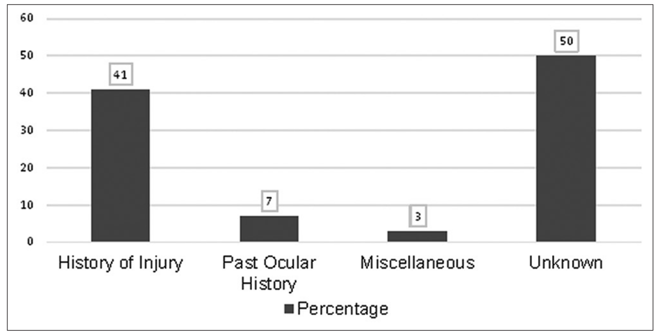

Figure 1: The predominant predisposing factors for infectious keratitis in the study population are shown, which include ocular trauma, preexisting ocular conditions, and unknown factors

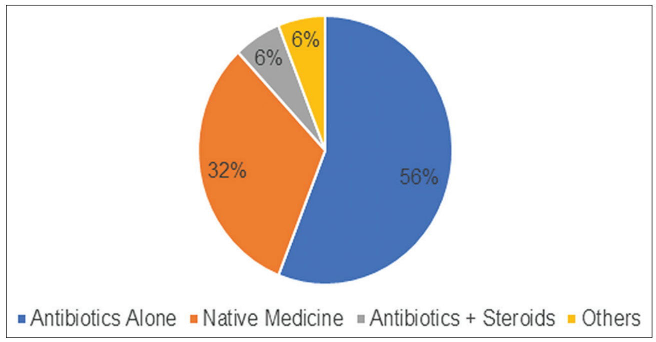

Figure 2: Previous treatment taken by patients in the form of antibiotics, native medications, and antibiotic–steroid combinations before presenting to the hospital

Five eyes (6.5%) had preexisting ocular conditions, such as epithelial basement membrane dystrophy in one eye (1.3%), vernal keratoconjunctivitis in one eye (1.3%), history of TPK in one eye (1.3%), and history of corneal tear repair in two eyes (2.7%). In case of the eye with previous keratoplasty, two loose sutures were found with sutural infiltrate, which had progressed to involve the graft–host junction. Miscellaneous risk factors like bathing in pond (1.3%) and welding arc exposure (1.3%) were also noted. With increasing use of overnight orthokeratology contact lenses for myopia control by children, contact lens usage is presenting as an important causative factor for infectious keratitis in older children in developed countries such as Taiwan and the USA. However, it is not commonly associated with infectious keratitis in developing countries.[7]

Thirty-four eyes (44.7%) had history of previous treatment before presenting to our hospital. Out of these, 19 (55.9%) had previous treatment with antibiotics, 11 (32.3%) had history of using native medicines, and two (5.9%) had used steroid–antibiotic combination eye drops. Fig. 2 depicts this data.

Central corneal involvement (central 2 mm zone) was found in 17 eyes (22.4%), paracentral (2–4 mm) involvement in 42 eyes (55.3%), peripheral involvement in nine eyes (11.8%), and diffuse involvement was found in eight eyes (10.5%). The size of infiltration ranged from 0.5 to 6 mm, with a mean (standard deviation [SD]) of 2.0 mm (1.3). Size of infiltration was <2 mm in 31 eyes (40.8%) and 2–6 mm in 45 eyes (59.2%). Infective keratitis was superficial in 47 eyes (61.8%) and extended to mid stroma in 26 eyes (34.2%). Deep stromal involvement was noted in three eyes (3.9%). Hypopyon was present in six eyes (7.9%) at the time of presentation.

Anterior uveitis was present in 29 eyes (38.2%) at the time of presentation, which resolved in all cases by the end of 1 week with intensive antimicrobial therapy and cycloplegics.

Microbiological analysis

Forty-eight (63.2%) of 76 eyes were smear positive, of which 26 eyes (54.2%) were KOH positive and 22 (45.8%) were gram positive.

Smear results are shown in Table 1 and culture results in Table 2.

Twenty-eight (36.8%) of 76 eyes were culture positive. Bacterial isolates were observed in five eyes (17.9%) and fungus in 23 eyes (82.1%). Bacterial isolates were subjected to antibiotic sensitivity; sensitivity to antifungals was not seen for fungal isolates. Also, 7.1% eyes were culture positive for *Streptococcus pneumoniae,* and *Pseudomonas aeruginosa* was also isolated from 7.1% eyes. *Fusarium* species (67.8%) were the most common pathogens resulting in fungal keratitis, followed by *Aspergillus* species (10.7%); pigmented fungus was also isolated in one case (3.6%). Fig 3 shows fusarium keratitis on presentation, fusarium colonies on agar and appearance post therapeutic keratoplasty. Nine (11.8%) out of 76 eyes were clinically diagnosed as viral keratitis. Viral keratitis was epithelial in eight patients, and non-necrotizing stromal keratitis was seen with epithelial keratitis in one patient, which was managed with a combination of topical and systemic antivirals and topical steroids. Conjunctival and corneal smears were sent for PCR in cases of viral keratitis, but all were negative. Fig 4 shows paediatric dendritic keratitis with branching pattern.

Mean (SD) of the duration of onset of growth in culture was 2.29 (1.0) days and ranged from 1 to 6 days. Topical antimicrobial therapy was given in all eyes as per the smear and culture results. Moxifloxacin 0.5% eye drops were started for all gram-positive cocci, irrespective of size. Additionally, in seven patients with ulcer size >2 mm, ciprofloxacin eye ointment 0.3% was started on twice-daily dosing. Out of smear-negative patients, 10 patients with ambiguous presentation were initially started on both moxifloxacin and natamycin. Two eyes (2.6%) needed surgical intervention in the form of TPK.

Outcome

Functional outcome was evaluated in terms of visual acuity and final outcome of the inflammation, whether healing occurred with scar tissue formation or further extension of the ulcer in size and depth, leading to perforation and other complications.

Visual acuity could not be assessed in two patients below 1 year of age. At the final follow-up, 65 out of 74 eyes (87.8%) achieved a best corrected visual acuity (BCVA) of 6/12 or better, eight eyes (10.8%) had BCVA between 6/24 and 6/60, and one eye (1.4%) had BCVA below 6/60.

The follow-up rate was 100% up to 3 months; therefore, no average calculation was done.

Visual acuity classification

McNemar–Bowker test was used to compare the categorical classification of follow-up visual acuity with baseline, which

Table 1: Corneal Scraping Results in Paediatric Infectious Keratitis

Smear results	Frequency (*n*)	Percentage (%)
Smear positive	48	63.2
KOH positive	26	54.2
Gram positive	22	45.8
Gram-positive bacilli	1	4.5
Gram-negative bacilli	5	22.7
Gram-positive cocci	7	31.8
Gram-positive cocci in pairs	5	22.7
Microsporidium	3	13.6
Acanthamoeba	1	4.5
Smear negative	28	36.8
Total	76	100

Table 2: Organisms isolated in Cultures in Paediatric Microbial Keratitis

Culture results	Frequency (*n*)	Percentage (%)
Culture positive	28	36.8
A. Fungus		
Fusarium	19	67.8
Aspergillus flavus	3	10.7
Pigmented fungi	1	3.6
B. Bacteria		
Pseudomonas aeruginosa	2	7.1
Corynebacterium	1	3.6
Streptococcus pneumonia	2	7.1
Culture negative	48	63.2
Total	76	100

Table 3: Visual Acuity assessment at Baseline and in successive follow ups

Visual acuity	Baseline	Week 1	Week 2	Month 1	Month 3
6/12 and better	47 (63.5)	54 (73.0)	59 (79.7)	60 (81.1)	65 (87.8)
Below 6/12-6/60	15 (20.2)	16 (21.6)	12 (16.2)	10 (13.5)	8 (10.8)
Below 6/60	12 (16.2)	4 (5.4)	3 (4.1)	4 (5.4)	1 (1.4)
Total	74	74	74	74	74
P	-	0.019	0.001	0.003	<0.001

Table 4: Comparison of baseline visual acuity with follow up visual acuity in log MAR form to look for significant difference

Visual acuity	*n*	Mean (SD)	Median logMAR	IQR	*P*
Baseline	74	0.44 (0.6)	0.18 (6/9)	0-0.48	-
Week 1	74	0.32 (0.4)	0.18 (6/9)	0-0.48	<0.001
Week 2	74	0.24 (0.3)	0.18 (6/9)	0-0.30	<0.001
Month 1	74	0.26 (0.5)	0 (6/6)	0-0.30	<0.001
Month 3	74	0.15 (0.3)	0 (6/6)	0-0.18	<0.001

IQR=interquartile range, logMAR=logarithm of minimum angle of resolution, SD=standard deviation

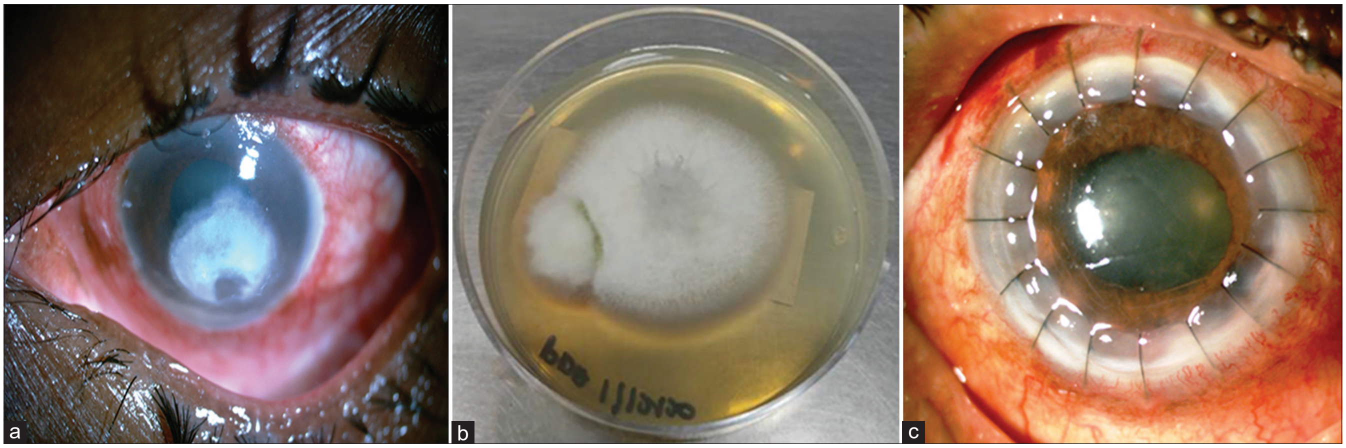

Figure 3: (a) Fungal corneal ulcer with feathery margins with involvement of deep stroma and stromal thinning. (b) Culture in potato dextrose agar showing colonies of Fusarium species with cottony white appearance. (c) Post-therapeutic keratoplasty of fusarium keratitis, with clear and well-apposed graft

Figure 4: Photograph of pediatric dendritic keratitis with characteristic branching pattern with terminal bulbs

is shown in Table 3. *P* value less than 0.05 was considered as statistically significant. A visual acuity of 6/12 and better was noted in 63.5% of the study subjects at baseline, 73% of subjects at week 1, ($P = 0.019$), 79.7% of subjects at week 2, ($P = 0.001$), 81.1% of subjects at 1 month ($P = 0.003$), and 87.8% of subjects at 3 months ($P < 0.001$).

For analysis, Snellen's visual acuity values were converted into logarithm of minimum angle of resolution (logMAR) values, as shown in Table 4. Wilcoxon signed rank test was used to find out the significant difference of follow-up visual acuity with baseline. *P* value less than 0.05 was considered as statistically significant. The *P* values showed there was a significant difference in visual acuity at week 1 ($P < 0.001$), week 2 ($P < 0.001$), month 1 ($P < 0.001$), and month 3 ($P < 0.001$).

Thirty-one eyes had an ulcer size of less than 2 mm and had complete resolution of infection with antimicrobial therapy. Also, 45 eyes had an ulcer size between 2 and 6 mm, of which perforation was noted in one eye (1.3%) and nonhealing ulcer was noted in one eye (1.3%). At the end of 3-month follow-up, 44 eyes (57.9%) healed with scar. Scarring with thinning was noted in 18 eyes with an ulcer size between 2 and 6 mm.

Discussion

Pediatric microbial keratitis accounts for approximately 13% of all cases of infectious keratitis and is more commonly observed in developing countries, especially in tropical regions.[7] According to Maurin *et al.*[8] the incidence of corneal-related blindness in children in tropical countries is 20 times higher than that in children from developed countries. Srinivasan *et al*.[9] reported that, in South India, ulceration of the cornea "is a blinding disease of epidemic proportions."

In our study, children of all age groups (ranging from 1 month to 16 years) were found to be affected by microbial keratitis. Higher incidence was found between 11 and 16 years of age (50.7%). Many authors have reported similar observations,[10-12] but the reason behind this is unclear, and studies involving larger population of children will be required to derive a conclusion.

Similar to other studies, in our study also, males were commonly affected than females,[13] with a male: female ratio of 1.5:1. In our study, 72.6% of children were from urban areas. This is in contrast to many other studies where children belonging to rural areas were reported to be at high risk.[14] This could be due to the fact that ours is a tertiary center located in an urban area, and therefore, higher case load was received from urban areas.

In our study, trauma was the leading predisposing factor for microbial keratitis, consistent with other studies from India, Iran, and Saudi Arabia.[13,15,16] Trauma was mostly caused by fingernail, stick, stone, pencil, and toys. This highlights the necessity for framing strict safety rules, especially in outdoor and indoor playgrounds for children. This is in contrast to western studies, where contact lens wear was the common risk factor for microbial keratitis. Rossetto *et al.*[17] reported wearing of contact lens as a predisposing factor in 77.6% of the cases, followed by ocular trauma (8.4%) and systemic factors (4.7%). This may be due to the relatively high prevalence of refractive errors and the popularity of contact lens use in these areas. Our study and other studies from India demonstrated that contact lens wear was a negligible predisposing factor in the development of microbial keratitis. This may be explained by the lower prevalence of contact lens use in Indian children, compared to western countries.

Many studies have reported preexisting ocular disease as a significant predisposing factor for microbial keratitis. Kunimoto *et al*.[11]and Ormerod *et al*.[2] reported vitamin A deficiency and other ocular surface disorders as the major risk factors for microbial keratitis. In our study, one patient with epithelial basement membrane dystrophy developed infective keratitis. Two eyes with previous history of corneal tear repair and one eye with previous penetrating keratoplasty developed microbial keratitis. Similar to our study, Kunimoto *et al*.[11] have reported previous penetrating keratoplasty as a risk factor in 8.8% eyes. Cruz *et al*.[12] and Clinch *et al*.[18] have also reported similar findings.

A significant number of eyes (44.7%) had history of previous treatment before presenting to our hospital, which included use of antibiotics alone (55.9%), antibiotic–steroid combination (5.9%), breast milk instillation (17.6%), and use of native herbal medicines (2.9%). In a study conducted in blind schools in Maharashtra,[19] 22.2% children had corneal blindness and one-third of the causes of blindness were preventable or from treatable causes. This highlights the need for creating public awareness regarding the risk factors and serious sight-threatening complications of microbial keratitis and the need to seek urgent treatment at an eye care center, avoiding local home-based remedies.

Culture positivity was obtained in 28 eyes (41.8%), with no polymicrobial isolates. This was lower than the values reported in other studies on microbial keratitis.[2,11,12,18] The reason for this may be due to previous antibiotic treatment before referral. Additionally, we scraped the cornea to take a specimen for smear first, which might reduce the microbial load remaining in the corneal lesion. Thus, the small amount of culture material available in corneal ulcer samples may not produce enough organism growth, especially in the small corneal ulcers.

Out of the culture-positive eyes, bacterial isolates were observed in five eyes (17.9%) and fungal isolates in 23 eyes (82.1%). This is in contrast to other studies, where gram-positive cocci, predominantly coagulase-negative *Staphylococcus* and *P. aeruginosa*, were the frequently isolated organisms.[2,11] Song *et al*.,[14] in a retrospective study conducted in Wuhan, China, reported that gram-positive cocci accounted for 41.0% of the isolates, predominated by coagulase-negative *Staphylococcus aureus* (35.9%), while fungi accounted for 48.7% of the isolates, and *Fusarium* species was the predominant pathogen in fungal keratitis. In a study done by Kunimoto *et al*.[11] in Hyderabad, fungal isolates accounted for 17.2% cases. These studies are pointing toward the fact that, even within the same country, the prevalence of fungi responsible for pediatric keratitis can vary. According to King *et al*.,[20] the prevalence of fungal keratitis in a region depends greatly on the climate. A hot, windy climate makes fungal keratitis more frequent in tropical areas. The higher rates of fungal keratitis in South Indian population may also be attributed to the agriculture-based livelihood, which can increase their vulnerability to ocular trauma and subsequent infection.

In our study, out of 76 eyes, nine were clinically diagnosed as viral. The mean age of presentation of viral keratitis was 11.5 years, ranging between 10 and 15 years. They were subjected to PCR of conjunctival and corneal smears, but all were negative. The probable reason for this was the use of topical antivirals before presentation to our clinic. According to Ma *et al*.,[21] after treatment, the percentage of herpes stromal keratitis HSK-positive samples is low in both corneal epithelium scrapings and in tears, giving a false-negative result. The sites from where samples were collected before the treatment clearly affect the percentage of positive results and the concentration of herpes simplex virus (HSV). The diagnostic accuracy can be improved if the medical material is collected from the corneal epithelium scrapings. The combination of laboratory detection of HSV DNA by real-time PCR and of HSV-sIgA by enzyme-linked immunosorbent assay (ELISA) using tear samples enables higher reliability in diagnosing the subgroups of Herpes Simplex keratitis (HSK).[22]

In our study, intensive antimicrobial therapy was given to all eyes. Topical antimicrobial application leads to high concentration of the drug at the infection site. Most of the eyes (97.4%) responded well with medical treatment alone. This is consistent with the results of similar studies on microbial keratitis in children. Parmar *et al*.[23] reported that microbial keratitis in pediatric patients was more likely to be nonsevere and had a better chance of resolution with medical therapy alone, when compared to that in the general adult population. Surgical intervention in the form of TKP was done in two eyes (2.6%). These two patients showed complete resolution of infection with clear graft at the final follow-up. No graft reinfection was noted after TPK. In the study by Rossetto *et al*.,[17] none of the patients required surgical intervention. High incidence of surgical intervention (15.9%) was reported by Kunimoto *et al*.[11]

At the final follow-up, 87.8% eyes had a visual acuity of 6/12 or better. Early diagnosis and appropriate treatment were the probable reasons for good visual acuity observed in these eyes.

Conclusion

We conclude that the demographic and clinical profile of pediatric microbial keratitis in this part of South India is relatively similar to that in other parts of India and other tropical countries in the world. Knowledge of regional patterns of infection and drug susceptibility is essential in ensuring prompt treatment of this potentially sight-threatening condition. Majority of cases responded well with medical management alone, with 87.8% eyes achieving a BCVA of 6/12 or better at the final follow-up. To conclude, we can say that early diagnosis, identifying the predisposing factors and etiological microbial organisms, intensive drug therapy, and timely surgical intervention can prevent profound visual morbidity in children. As the study was carried out in a tertiary eye care hospital in South India, the results of the same cannot be generalized. It retains its regional significance.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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