Graft infection following corneal transplantation, though more common in the developing world, may jeopardize the graft survival, and at times, lead to the dreaded complication, i.e., endophthalmitis. Its incidence is quite variable with the type of corneal transplantation and is 1.76–7.4%, 0.2–0.5%, and 7% following penetrating keratoplasty (PK), Descemet stripping endothelial keratoplasty (DSEK), and keratoprosthesis, respectively. The infective agents have traditionally been linked to climatic conditions and geographical locations. Though the literature is scant from India, the two largest series of graft infections following PK depict coagulase-negative Staphylococcus as the most commonly isolated bacterium, whereas among fungi, Aspergillus spp. has been incriminated as the most common organism followed by Fusarium spp. responsible for the graft infection. None of the graft infections was due to Candida spp. in the latest series. Similarly, bacteria and filamentous fungi have been held responsible for graft infection following DSEK and keratoprosthesis, as highlighted in the largest series from India.

The Candida infection following corneal transplantation is rarely being reported from India. An extensive MEDLINE search has revealed only one case report, being published over the last two decades. However, with the current cluster of Candida infection at two centers, we have observed a huge gap in our understanding regarding the natural history of Candida-induced keratitis following corneal transplantation, and the current study is primarily aimed to fill this gap with the incorporation of risk factors, clinical features, management, and outcome of this rare infection in the developing world. To the best of our knowledge, this is the largest series of graft infections by Candida sp., being reported from India at the current time.

**Methods**

This study strictly adhered to the tenets of the Declaration of Helsinki, and prior approval of the institutional review boards have been taken. We did a clinical and microbiological review of the graft infection in 789 medical records, in patients who underwent corneal transplantation (PK/DSEK/Descemet membrane endothelial keratoplasty (DMEK)/deep anterior lamellar keratoplasty (DALK)/Keratoprosthesis) from April 2015 to March 2020 at two tertiary eye care facilities in India. Out of the 789 records of the patients of corneal transplantation...
and keratoprosthesis, 31 patients (3.92%) developed infectious keratitis of which 5 eyes (16.12%) were found to have an infection with Candida spp., which have been included in our study.

The medical records were reviewed for demographics, risk factors for graft infection, indication, number and types of corneal transplantation, time of onset of infection following corneal transplantation, characteristics of the infective lesion, corneal scraping results including smear, culture, and antifungal sensitivity, treatment plan including the types of antifungals, dosage, and the duration of administration, time to healing following drug administration, and the final outcome following management.

A cornea service protocol was followed in all the patients. Initially, a detailed history was taken including the risk factors such as the multiple corneal interventions, presence of the epithelial defect, and the prolonged usage of topical steroid/antibiotic. Following the history, visual acuity was assessed by Snellen’s visual acuity chart. Then, a thorough slit-lamp examination was performed to assess the location and extent of both the epithelial defect and the infiltrate, the height of hypopyon, graft clarity, the status of the sutures, lenticule and interface in DSEK, and the prosthesis status in the patients with keratoprosthesis.

The corneal scrapings of the lesion were obtained and subjected to both the smear preparation and culture. The smears were prepared for the Potassium Hydroxide (KOH) mount and Gram’s stain. The culture was performed on media including sheep blood agar, 5.0% chocolate agar, and Sabouraud dextrose agar. All media were incubated aerobically at 37°C except the Sabouraud dextrose agar which was incubated at 25°C for 2 weeks. The genus level identification was achieved by the above-mentioned techniques whereas the species level identification in some patients, in addition to the antifungal sensitivity, was aided by a yeast reagent card on VITEK 2 compact automated microbiology system (Biomerieux, France) with 99% probability.

Based on the antifungal sensitivity report, the antifungals were administered in some of the patients. All the patients were administered topical antifungals like natamycin 5%/flucnazo 0.3%, and voriconazole 1%. Tablet fluconazole was administered to some of them. The response to the above management was assessed. Some responded and some did not and had to undergo further interventions.

Statistical analysis
Data analysis was done by using SPSS (Statistical Package for Social Sciences) version 20.0. The mean, standard deviation (SD), and frequency (percentage) were used to describe the summary data. A P value <0.05 was considered as significant.

Results
Demographics
The median age of the subjects with the Candida graft infection was 62.4 ± 10.33 years (range, 62–71 years). All the patients were males. The right eye was involved in three patients whereas the left eye was involved in two patients. The keratoprosthetics patients were aphakic whereas the remaining three were pseudophakic [Table 1].

Risk factors
The risk factors [Table 1] of the Candida infection in the current series include repeat corneal transplantation, presence of an epithelial defect, and the long-term use of topical steroids, antibiotics, cyclosporine, and bandage contact lens. Repeat corneal transplantations were seen in four out of five subjects. PK was performed four times in two patients and three times in one patient. DSEK was conducted thrice in one patient. Out of four patients with repeat corneal transplantation, keratoprosthesis was performed twice in one patient and once in another patient. The epithelial defect was noted in three out of four patients. The long-term use of topical steroids was seen in all the patients. The average duration of topical steroid administration from the latest corneal transplantation was 4.8 ± 0.83 months (range, 4–6 months). Eyedrop dexamethasone 0.1% was administered in four patients whereas eyedrop difluprednate 0.5% was instilled in one patient.

The long-term use of topical antibiotic administration was seen in two patients. In one patient, a combination of fortified vancomycin 50 mg/mL and moxifloxacin 0.5% was administered for 6 months whereas in another, a combination of fortified vancomycin 50 mg/mL, moxifloxacin 0.5%, and chloramphenicol 0.3% was instilled for 5 months. Long-term topical cyclosporin 2% was administered in one patient for 4 months. Bandage contact lens was applied in one patient for 6 months. The ocular surface and tear film status were normal in all five patients. None of the patients had any systemic disease making the eye prone to corneal infection.

Clinical characteristics
The average duration of the Candida corneal infection from the latest corneal transplantation was 4.8 ± 0.83 months; range
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4–6 months. The clinical features of the *Candida* graft infection are depicted in Table 2 and in Fig. 1a-f.

**Diagnosis**

Corneal smear on potassium hydroxide (KOH) wet mount exhibits multiple, round to oval, large, budding cells suggestive of the *Candida* species in three subjects whereas the Gram stain smear at X100 magnification shows multiple, gram-positive, budding cells with similar morphology as described above in the two patients. The culture on chocolate agar exhibits confluent white colonies with discrete margins 24 h after incubation at 37°C in four out of five patients [Fig. 2]. The species were identified as *Candida parapsilosis* and *Candida pelliculosa* in two out of five patients. This was done on the VITEK-2 compact system. *Candida parapsilosis* was found sensitive to fluconazole (MIC: ≤0.5), voriconazole (MIC: ≤0.2), capsofungin (MIC: 1.0), micafungin (MIC: 2.0), amphotericin B (MIC: 0.5), and flucytosine (MIC: ≤0.1) whereas *Candida pelliculosa* was found sensitive to fluconazole (MIC: 1.3), voriconazole (MIC: 0–0.12), capsofungin (MIC: 0.21), amphotericin B (MIC: 0.3), and flucytosine (MIC: ≤1.0) [Table 2].

**Treatment**

In two patients, oral fluconazole (150 mg) was administered twice daily whereas, in one, it was administered daily for 5 days followed by a once-a-week for a total of three dosages. Topical fluconazole (0.3%) was administered in three out of five patients whereas topical voriconazole (1%) was instilled in the remaining two patients. Natamycin 5% was administered in one patient. Topical antibiotic (moxifloxacin 0.5%) was also administered in patients with keratoprosthesis [Table 2].

**Outcomes**

The time to healing from the beginning of antifungals in five patients was 4.66 ± 1.96 weeks; range, 3–8 weeks. Two patients achieved 1/60 Snellen visual acuity after healing of the *Candida* keratitis. Three patients developed endophthalmitis [Fig. 3]. Out of the three, two required evisceration, whereas the third one could not be followed for more than 1 week as he succumbed to myocardial infarction [Table 2].

**Discussion**

The literature is extremely scant in post-corneal transplant *Candida* keratitis in India. In 1995, Satpathy *et al.*[4] reported *Candida spp.* as a causative agent in 6 out of 1,157 fungal graft infections post-keratoplasty. In 2002, Vajpayee *et al.*, in one of the largest series of post-keratoplasty infectious keratitis, reported that none of the graft infections was due to *Candida spp.* In 2014, Basak *et al.*, in a series of 430 DSEK.
cases, reported one patient of interface infection with Candida spp. in an early postoperative period and two patients with Candida keratitis in the late postoperative period. In 2016, Sharma et al. reported Candida infection in 1 out of 10 patients with the end-stage corneal disease who had undergone implantation of Auro keratoprosthesis. Subsequently, in 2018, there existed a case report from India reporting graft infection due to Candida glabrata following a successful optical keratoplasty. The current series of Candida keratitis, to the best of our knowledge, is the largest in recent time, highlighting the clinical characteristics and management outcome following the varied forms of corneal transplantation.

The risk factors predisposing to graft infection following corneal transplantation include contaminated donor tissue, ocular surface disorder, recurrence of the previous infection, chronic steroid and antibiotic usage, contact lens usage, diabetes mellitus, loose suture, persistent epithelial defect, decompensated graft, and graft hypoesthesia. Though multiple risk factors have been stated in the literature for graft infection, what is common in all of our patients is repeat surgeries. We presume that the repeat surgeries make the graft a high risk, hence, more chances of graft rejection and thereby corneal decompensation. This is a vicious cycle as corneal decompensation invariably leads to epithelial defect, and thus, graft infection. In addition, repeat surgeries expose the patients to chronic use of topical steroids and antibiotics, thereby, not only reducing the localized immunity but altering the milieu of the ocular surface and making the graft prone to infection. Long-term continuous use of bandage contact lens (BCL) as seen in patient 1 and chronic use of topical cyclosporin as observed in patient 2, might be the contributing factors for Candida keratitis. We believe that BCL invites infection by providing nidus for the infective agents either in the cracks or in the protein deposits due to prolonged wear whereas topical cyclosporin promotes infection by suppressing the localized immunity.

We presume that it is the repeat grafts and the long-term use of topical steroids that are the main contributing factors for the Candida infection in our cases. The source of Candida species is probably the skin or conjunctiva, where it lives as a harmless commensal. What we foresee that the pathogenesis in our cases involves the adherence of yeast cells to the corneal substrate through the epithelial defect followed by the biofilm formation. The biofilm provides a stable environment to the organisms and protects them from the local host immune mechanism and also from external aggression in the form of topical medication. In one of our cases, due to localized immunosuppression, the seeded Candida parapsilosis became the sessile pathogen, surrounded by the biofilm, allowing its gradual spread across the lamellae with limited surrounding inflammation, resulting in discrete keratitis with a crystalline pattern.

The literature has described varied manifestations of the Candida infection following corneal transplantation. Following PK, the manifestations can either be in the form of infectious crystalline keratopathy (ICK) or multiple stromal infiltrates. Multiple white interface infiltrates have been described following Descemet Stripping Automated
Endothelial Keratoplasty (DSAEK).\(^\text{8,21}\) Following DALK, the manifestations can either be in the form of ICK or white cord-like deposits/small cream-colored plaques/or multiple infiltrates at the graft-host interface.\(^\text{22‑25}\) In Boston type I keratoprosthesis, the Candida infection invariably presents either as a white opacity under the edge of the anterior plate of keratoprosthesis or infiltrate surrounding the optic of the prosthesis with an overlying corneal melt.\(^\text{26,27}\) Unlike the description in the literature following a repeat PK, what we have observed in our series is the powdery deposits or the pearly white infiltrate involving the anterior surface of the corneal stroma. Similarly, unlike the interface deposits, we have observed ICK at the host corneal surface in our series. In line with the literature, we have observed white plaque adjacent to the optic cylinder in one of the patients whereas powdery deposits in another patient. What we have found is that the current series adds a plethora of Candida manifestations in addition to the manifestations existing in the literature.

The outcomes of the Candida infection following corneal transplantation are quite variable in the literature. Following PK, the prognosis, like in our cases, is invariably grim as patients do not respond to medical management and ultimately require repeat surgical intervention.\(^\text{19,20}\) Unlike our cases, Candida infection following DSEK, which predominantly involves the interface and medical management in such cases, like following PK, is invariably unsuccessful.\(^\text{29}\) The prognosis of Candida keratitis following keratoprosthesis is also not very encouraging in our series. Kim \textit{et al.}\(^\text{26}\) have clearly stated that infectious keratitis including Candida keratitis following keratoprosthesis seemed to respond to medical management in 47% of the cases and the remaining 53% of the cases required either the replacement of keratoprosthesis or therapeutic keratoplasty. It is to reiterate that the poor outcome in three out of five cases in our series skews the picture because two were keratoprosthesis patients with single chambers and it is a well-known fact that single chambers lead to an early spread to infection to the vitreous, thus, poor prognostication.

**Conclusion**

To conclude, Candida keratitis following corneal transplantation, though unusual in India, seems to be an emerging presentation and can easily be avoided by a timely reduction of the risk factors. Since a plethora of clinical presentations are associated with Candida spp., it is prudent to have a definitive diagnosis and sensitivity pattern for successful management.

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**Conflicts of interest**
There are no conflicts of interest.

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