Interface infectious keratitis after anterior and posterior lamellar keratoplasty. Clinical features and treatment strategies. A review

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ABSTRACT
Interface infectious keratitis (IIK) is a novel corneal infection that may develop after any type of lamellar keratoplasty. Onset of infection occurs in the virtual space between the graft and the host where it may remain localised until spreading with possible risk of endophthalmitis. A literature review identified 42 cases of IIK. Thirty-one of them occurred after endothelial keratoplasty and 12 after deep anterior lamellar keratoplasty. Fungi in the form of *Candida* species were the most common microorganisms involved, with donor to host transmission of infection documented in the majority of cases. Donor rim cultures were useful to address the infectious microorganisms within few days after surgery. Due to the sequestered site of infection, medical treatment, using both topical and systemic antimicrobials drugs, was ineffective on halting the progression of the infection. Injection of anti-fungals, right at the graft–host interface, was reported successful in some cases. Spreading of the infection with development of endophthalmitis occurred in five cases after Descemet stripping automated endothelial keratoplasty with severe sight loss in three cases. Early excisional penetrating keratoplasty showed to be the treatment with the highest therapeutic efficacy, lowest rate of complications and greater visual outcomes.

INTRODUCTION
Microbial infection of a corneal transplant is a complication that is a bane to all corneal surgeons, the sequelae of which can be devastating. Although infrequent, in the early postoperative period, keratitis after keratoplasty may threaten corneal graft- clarity and result in severe vision loss and, in worst cases, may cause endophthalmitis with potential need for enucleation. During the last two decades, lamellar keratoplasty (LK), in the forms of anterior lamellar keratoplasty (ALK) and endothelial keratoplasty (EK), has largely supplanted penetrating keratoplasty (PK) for selective replacement of the diseased corneal stroma or damaged endothelium.1 Advantages of these techniques are reduced risk of allograft rejection, shorter postoperative steroid treatment, early removal of sutures, no ‘open-sky’ surgery and preservation of globe integrity.2 All these benefits contribute to the reduced risk of early and late complications occurring after LK when compared with PK. Common feature to all LK procedures is the formation of a surface of contact between the donor graft and the recipient bed, namely, graft–host interface.3 Infection arising at this anatomical level represents a rare peculiar complication that may develop after all forms of LK. Diagnosis and treatment of this type of keratitis is a challenge for the surgeon due to the sequestered location of the infection in the deep stroma, with impaired access for microbiological testing and penetration of antimicrobial drugs. For these reasons, diagnosis of the infectious agent may be delayed or remain presumptive and treatment is often initiated empirically.

Cases of corneal interface infection after both anterior and posterior lamellar keratoplasty are reported in the literature. Due to its infrequent occurrence, knowledge of this new form of infection is limited and treatment strategies as well as clinical outcomes widely vary according to different authors. The purpose of this review is to describe the clinical features of interface infectious keratitis (IIK) occurring after ALK and EK and to analyse the treatment outcomes in order to establish a rationale for therapy.

METHOD OF LITERATURE SEARCH
We searched PubMed database (1949–2018) and Ovid Medline (1946–2018) for peer-reviewed publications relevant to the topic of corneal interface infection following lamellar keratoplasty. Key words included: keratitis, corneal interface infection, deep anterior lamellar keratoplasty (DALK), endothelial keratoplasty (EK), Descemet stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK). We did not use any date or language restrictions in the electronic searches. Articles in all languages were considered, provided that the non-English articles included English abstracts. The last electronic search was made on June 2018. Data on patients anagographic, keratoplasty procedure, time to onset of infection, microorganism isolates, therapy and visual acuity were compiled using Microsoft Excel software V.15.25 (Microsoft, Redmond, Washington, USA) and summarised using SPSS software V.20 for Microsoft Windows.

RESULTS
The literature search retrieved 122 titles and abstracts in English or with English translations. All papers available were reviewed by two authors (LF and EM) to check for adherence to the topic...
interface infection following lamellar keratoplasty. We selected 18 single case reports and eight case series of patients who developed infection originating at the graft–host interface after anterior or posterior LK. Cases where onset of infection did not originate in the graft–host interface were omitted. Single cases, part of case series, not referable to IIK were excluded from the analysis (ie, Tsui et al cases 1, 2, 3, 4, 5, 8, 9).

Patient characteristics and clinical outcomes of all cases included in this review are reported separately in tables 1 and 2 according to the type of surgery: DALK and EK. In the latter group, we included patients who underwent either DSAEK or DMEK.

Deep anterior lamellar keratoplasty

Twelve cases (11 case reports)14–15 of IIK, developed after DALK, are reported in the literature since 1999 (table 1). The causative microorganism was Candida spp in seven cases (63%) and Klebsiella pneumoniae, Rhodotorula spp, Actinomyces spp and Mycobacterium spp in four cases. Infectious organisms were identified from cultures of the excised donor buttons in 10 cases and from the liquid employed to rinse the graft–host interface in one case. Donor rim cultures, obtained in five cases, resulted negative in two cases and positive in three cases, with correspondence to the organisms identified in the recipients. Culture results were available 5–7 days after surgery.

The median time to development of clinical infection, calculated for all patients, was 29 days (range 2–120 days). Infection was managed initially with topical and systemic antifungals in combination with antibiotics. The choice of a specific drug was made on the available information resulting from donor rim cultures, obtained in five cases, and positive in three cases, with correspondence to the organisms identified in the recipients. Culture results were available 5–7 days after surgery.

Endothelial keratoplasty

Thirty-one cases (17 case reports)16–33 of IIK, developed after EK, are reported in the literature since 2009 (table 2). Twenty-nine of these occurred after DSAEK and two after DMEK. Infectious microorganisms were identified in 28 patients from cultures of the explanted donor lenticules (15 cases) or from aqueous and vitreous taps (13 cases). The remaining three cases were diagnosed and treated empirically as fungal infection on the basis of their clinical appearance.34,35 Candida spp was isolated in 21 specimens (75%) and Aspergillus fumigatus in one case, while bacteria in the form of Staphylococcus aureus (two cases), Staphylococcus epidermidis (one case), Enterococcus faecalis (one case) and Nocardia spp (one case) were identified in the remaining patients. Donor rim cultures, obtained in 28 cases, resulted negative in 13 cases and positive for Candida spp in the other 15 cases. Correspondence between the infectious microorganisms isolated from specimens and the ones cultured from positive donor rim was found in all patients.

The median time to development of clinical infection, in these patients, was 28 days (range 1–120 days). Rim cultures results became available after a median time of 5.5 days (range 3–14 days) after surgery. Despite combined topical and systemic antifungals, medical treatment alone was unsuccessful in halting the progression of the infection in all except one case.35 Surgical intervention by means of lenticule removal, intracameral and/or intravitreal antifungals injections and eventually PK was required to eradicate the infection in the majority of patients. In three cases, regression of infection was obtained with multiple intrastromal injections of amphotericin B (5 mg/mL) or voriconazole (50 mg/mL) inoculated closest possible to the graft–host interface, causing temporary focal graft detachment.34,35

Of all patients, five (16%) developed endophthalmitis and required pars plana vitrectomy and three (9%) developed surgical postoperative complications with severe sight loss. Median BSCVA measured 4–12 months after resolution of infection was 20/40 (range 20/500–20/20).

DISCUSSION

IIK represents a subset of infectious keratitis originating at the graft–host interface and occurring exclusively after LK procedures. A recent report of the Eye Bank Association of America34 encompassing 4 years (2017–2010) of activity, reported a cumulated frequency of postkeratoplasty infection of 0.026% for fungal and bacterial agents together, with a higher rate of fungal isolates (63%). The frequency of fungal infections after LK was nearly the double than PK, being 0.023% and 0.012%, respectively. The rate of fungal infection after anterior lamellar keratoplasty was 0.052% and 0.022% after EK. According to this report, there might be an increasing trend of occurrence of postkeratoplasty fungal infection since the introduction of EK as the procedure of choice for the treatment of corneal endothelial failure. A single-centre review of 1088 consecutive DSAEK surgeries, over an 8 years time lapse, reported 10 (0.92%) cases of interface infection, seven of them with culture positive results.23 We should consider that the overall perception of an increased risk of fungal infection after PK may be the consequence of over-reporting a novel complication occurring after a new surgical procedure. Due to the lack of a physiological hypothesis, whether IIK may represent a significant threat after LK remains yet to be defined.

Tissue manipulation either in the eye bank or in the operating room does not seem to influence the postoperative risk of bacterial or fungal infection.34,35 In our review, postoperative interface keratitis occurred using tissues for EK prepared either by surgeons in the operating room (13 cases) or by eye bank technicians (eight cases). Correlation between recipient and donor rim isolates was found for most of the tissues prepared in eye banks, indicating the donor and not the processing as the source of infection. In this respect, Brothers et al16 demonstrated that tissue warming during EK processing is responsible for promoting Candida growth in donor rims, advocating antifungal drug supplementation of storage media. Ritterband et al37 proved the efficacy of added voriconazole to Optisol GS on reducing the rate of positive rim cultures. Organ culture is the preferred method of cornea preservation in Europe. With this storage method, prolonged storage time allows to conduct routine microbiology tests and to identify and discard contaminated corneas before they are issued for transplantation.38 To date, lack of strong evidence of effectiveness of antifungals in storage media kept at hypothermic temperature (2°C–8°C), along with doubts regarding safety for the corneal endothelial cells, are presently not advising the addition of antifungals to cold storage media.34
Table 1 Literature review of clinical cases and case series of interface keratitis following DALK

| Patients (n) | Age (years) | Microorganism isolated from specimens | Time to infection onset (day) | Donor rim culture | Time to positive donor rim culture report (day) | Medical treatment topical and/or systemic | Surgical treatment | Endophthalmitis | Visual outcome (BSCVA Snellen) | Postoperative complications |
|--------------|-------------|---------------------------------------|------------------------------|-------------------|-----------------------------------------------|------------------------------------------|-------------------|----------------|-----------------|-------------------------------|
| 1            | 55          | Rhodotorula sp (donor button + interface biopsy) | 5               | nr                | nr                                           | Topical natamycin 5% Amphotericin B 0.15% | Donor button exchange | None            | nr              | No                           |                               |
| 6            | 30          | *Candida albicans* (donor button)         | 28              | *C. albicans*     | 5                                           | Topical amphotericin B (3 mg/mL) Liposomal amphotericin B (3 mg/kg) IV | Donor button exchange + interface amphotericin B (5 µg/0.1 mL) PK | None            | 20/25            | No                           |                               |
| 2            | 21          | *Candida glabrata* (donor button)         | 60              | nr                | nr                                           | Topical amphotericin B, oral ketoconazole 400 mg once in a day, Natamycin 5%, oral ketoconazole 400 mg once in a day | Interface irrigation with DM rupture PK | None            | nr              | No                           |                               |
| 35           | 30          | *Klebsiella pneumoniae* (donor button)    | 6               | nr                | nr                                           | Topical vancomycin (50 mg/mL), cefazidime (50 mg/mL) | PK               | None            | 20/20            | No                           |                               |
| 1            | 21          | *Actinomyces species* (donor button)      | 6               | nr                | nr                                           | Topical ofloxacin 0.3%, betamethasone 0.1% + chloramphenicol 0.25%, amphotericin B PK PK graft exchange | None            | 20/25            | No                           |                               |
| 1            | 23          | *Candida species* (donor button)          | 30              | Not performed     | na                                           | Topical amphotericin B (5 µg/mL), cefuroxime (1 mg/mL) Liposomal amphotericin B (3 mg/ml) IV Oral itraconazole 200 mg OD | Interface irrigation DM rupture PK | None            | nr              | No                           |                               |
| 1            | 18          | *C. albicans* (irrigation liquid)         | 120             | Negative          | nr                                           | Topical cefazidime (50 mg/mL), vancomycin (50 mg/mL), natamycin 5% | Interface irrigation (amphotericin B 0.15%) DM rupture | None            | 20/30            | No                           |                               |
| 1            | 39          | *Candida orthopsilosis* (donor button)    | 5               | Yeasts            | 6                                           | Topical voriconazole, oral voriconazole 400 mg two times a day | Interface irrigation voriconazole (0.25 mg/mL) + amphotericin B (0.5 mg/mL) PK | None            | 20/630           | No                           |                               |
| 1            | 26          | *Atypical Mycobacterium* (donor button)   | 90              | nr                | nr                                           | Topical amikacin 2.5% | Donor button exchange PK | None            | 20/40            | No                           |                               |
| 1            | 31          | *C. glabrata* (donor button)              | 6               | Medium culture negative Donor rim culture not performed | nr                                           | Topical levofloxacin 0.5%, fluconazole 0.5% | Interface irrigation cefturoxime 5% + fluconazole (0.8 g/L) donor button exchange PK | None            | 20/40            | No                           |                               |
| 1            | 32N         | Negative                                  | 90              | nr                | nr                                           | Topical voriconazole, natamycin, oral itraconazole 100 mg twice a day | None | None            | 20/80            | Leukomatus scar              |                               |

BSCVA, best spectacle corrected visual acuity; DM, Descemet membrane; PK, penetrating keratoplasty; na, not applicable; nr, not reported.
Table 2  Literature review of clinical cases and case series of interface keratitis following DSAEK and DMEK

| Patients (n) | Age (years) | Type of surgery | Donor preparation | Microorganism isolated from specimens | Time to infection onset (days) | Donor rim culture | Time to positive donor rim culture (days) | Medical treatment topical and/or systemic | Surgical treatment | Endophthalmitis (BSCVA Snellen) | Visual outcome (BSCVA Snellen) | Postoperative complications |
|-------------|-------------|-----------------|-------------------|---------------------------------------|-------------------------------|-----------------|-------------------------------------------|------------------------------------------|-----------------|-------------------------------|---------------------------|-----------------------------|
| Koenig et al. [10] | 1 | 80 | DSAEK | Uncut | Candida albicans (donor lenticule) | 7 | C. albicans | 5 | None | Donor lenticule removal then PK | No | NPL | Photis bulbi |
| Kitzmann et al. [11] | 2 | 80 | DSAEK | nr | C. albicans (aqueous tap) | 39 | C. albicans, Candida glabrata, Staphylococcus | 3 | Topical amphotericin B 0.15% Oral fluconazole 200 mg two times a day | Donor lenticule exchange + intracameral amphotericin B 8 (5 µg/0.1 mL) | No | 20/50 | No |
| | 80 | DSAEK | nr | C. albicans (anterior corneal infiltrate scraping) | 41 | C. albicans, Candida glabrata, Staphylococcus | 3 | Topical amphotericin B 0.15% Oral fluconazole 200 mg two times a day | Intracameral amphotericin B 8 (5 µg/0.1 mL) x 2 Intravitreal amphotericin B 8 (10 µg/0.1 mL) | No | 20/40 | No |
| Chew et al. [12] | 1 | 72 | DSAEK | Uncut | C. parapsilosis (aqueous and vitreous tap) | 2 | Negative | na | Topical amphotericin B 8 (1 mg/mL) Oral voriconazole 200 mg two times a day | Intravitreal amphotericin B 8 (0.1 mg/mL) x 3 PK + vitrectomy | Yes | 20/40 | No |
| Lee et al. [13] | 2 | 81 | DSAEK | Precut | C. glabrata (donor lenticule) | 30 | C. glabrata | 3 | Topical amphotericin B 0.15% Oral voriconazole 200 mg two times a day | PK + intravitreal amphotericin B 8 (10 µg/0.1 mL) | No | 20/25 | No |
| | 76 | DSAEK | Uncut | C. albicans (corneal scraping) | 21 | Negative | 7 | Topical amphotericin B 0.15% Oral fluconazole 200 mg two times a day | PK | No | NPL | Supra chorioidal haemorrhage |
| Ortiz-Gomariz et al. [14] | 1 | 76 | DSAEK | Uncut | C. albicans (donor lenticule, aqueous and vitreous taps) | 90 | Not tested | na | Voriconazole 200 mg two times a day Intravenous voriconazole | Donor lenticule removal + vitrectomy PK + trabeculectomy | Yes | 20/00 | No |
| Sharma et al. [15] | 1 | 62 | DSAEK | nr | Aspergillus fumigatus (donor lenticule) | 30 | Negative | na | Natamycin 5% Voriconazole 200 mg two times a day | PK | No | 20/40 | No |
| Yamazoe et al. [16] | 1 | 74 | DSAEK | nr | C. albicans (aqueous tap) | 34 | C. albicans | nr | Topical voriconazole 1% + micafungin 0.1% Intravenous voriconazole 200 mg two times a day | Donor lenticule removal + posterior stroma debridement 4 months later PK + gonioplasty + intraocular lens exchange | No | 20/22 | No |
| Holt et al. [17] | 2 | 69 | DSAEK | Precut | C. albicans (donor lenticule) | 7 | C. albicans | nr | Topical amphotericin B 8 + voriconazole Oral fluconazole 200 mg two times a day | Donor lenticule removal Intracameral amphotericin B 8 (5 mg/mL) + vancomycin (1 mg) + ceftazidime (2.2 mg) PK + glaucoma tube | No | 20/30 | No |
| | 54 | DSAEK | Precut | C. albicans (donor lenticule) | 49 | C. albicans | nr | Topical amphotericin B 8 (2 mg/mL) + voriconazole 1% Intravenous voriconazole 200 mg two times a day | Intravitreal amphotericin B 8 (5 µg/0.1 mL) x 4 Lenticule removal PK | No | 20/80 | (previous RD surgery) No |
| | | | | | | | | | | | | | | |
| Tu et al. [18] | 2 | 66 | DSAEK | nr | Not assessed | 90 | Negative | na | Oral voriconazole 100 mg | Donor lenticule removal Intracameral voriconazole 8 (5 mg/mL) Intravitreal voriconazole 50 mg/mL weekly for 3 weeks | No | 20/500 | Corneal oedema |
| | 70 | DSAEK | nr | Not assessed | 49 | Negative | na | Oral voriconazole 100 mg | | | | |

Continued
Table 2 Continued

| Authors          | Patients (n) | Age (years) | Type of surgery | Donor preparation | Microorganism isolated from specimens | Time to infection onset (days) | Donor rim culture | Time to positive donor rim culture report (days) | Medical treatment topical and/or systemic | Surgical treatment | Endophthalmitis limits | Visual outcome (BSCVA, Snellen) | Postoperative complications |
|------------------|--------------|-------------|-----------------|-------------------|----------------------------------------|--------------------------------|-------------------|-----------------------------------------------|------------------------------------------|-------------------|------------------------|-----------------------------|--------------------------|
| Nahum et al.     | 7            | 52          | DSAEK for all cases | Uncut for all cases | Candida parapsilosis, Staphylococcus aureus | 112                           | Negative for all cases | na for all cases | Same treatment for all patients. Topical fortified antibiotics and antifungals. | | | 20/20                   | No |
|                  | 83           | 75          | DSAEK            | Uncut for all cases | Candida parapsilosis (donor lenticule) | 56                            | Negative for all cases | na for all cases | Same treatment for all patients. Topical fortified antibiotics and antifungals. | | | 20/100                  | No |
|                  | 67           | 70          | DSAEK            | Uncut for all cases | Nocardia species                      | 21                            | Negative for all cases | na for all cases | Same procedure for all patients. PK-intraocular amphotericin B, amikacin, vancomycin, cefazolin | | | 20/20                   | No |
|                  | 70           | 42          | DSAEK            | Uncut for all cases | Staphylococcus                          | 112                           | Negative for all cases | na for all cases | Same procedure for all patients. PK-intraocular amphotericin B, amikacin, vancomycin, cefazolin | | | 20/90                   | No |
| Wenget al.       | 1            | 80          | DSAEK nr         | Uncut for all cases | Candida glabrata (donor lenticule and vitreous tap) | 28                            | Positive for all cases | na for all cases | Same treatment for all patients. Topical fortified antibiotics and antifungals. | | | 20/20                   | No |
| Houssein et al.  | 1            | 45          | DSAEK nr         | Uncut for all cases | Candida glabrata                      | 1                             | Positive for all cases | na for all cases | Same procedure for all patients. PK-intraocular amphotericin B, amikacin, vancomycin, cefazolin | | | 20/100                  | No |
| Villasubia et al.| 1            | 73          | DSAEK Uncut      | Uncut for all cases | Candida glabrata                      | 10                            | Positive for all cases | na for all cases | Same procedure for all patients. PK-intraocular amphotericin B, amikacin, vancomycin, cefazolin | | | 20/100                  | No |
| Tsui et al.      | 2            | 85          | DSAEK Precut     | Uncut for all cases | Candida glabrata                      | 20                            | Positive for all cases | na for all cases | Same procedure for all patients. PK-intraocular amphotericin B, amikacin, vancomycin, cefazolin | | | 20/100                  | No |
| Wilde et al.     | 1            | 57          | DSAEK Uncut      | Uncut for all cases | Scopulariopsis gracilis               | 2                             | Positive for all cases | na for all cases | Same procedure for all patients. PK-intraocular amphotericin B, amikacin, vancomycin, cefazolin | | | 20/100                  | No |
| Thompson et al.  | 1            | 75          | DMEK Prestripped | Uncut for all cases | Candida glabrata                      | 8                             | Positive for all cases | na for all cases | Same procedure for all patients. PK-intraocular amphotericin B, amikacin, vancomycin, cefazolin | | | 20/100                  | No |
| Tu et al.        | 1            | 61          | DMEK nr          | Not assessed                         | Candida glabrata                | 30                            | Positive for all cases | na for all cases | Same procedure for all patients. PK-intraocular amphotericin B, amikacin, vancomycin, cefazolin | | | 20/100                  | No |
| Portet et al.    | 1            | 68          | DSAEK nr         | Enteroctococcus faecalis             | 120                           | Not tested                      | na for all cases | Same treatment for all patients. Topical fortified antibiotics and antifungals. | | | 20/100                  | No |
| Palioura et al.  | 2            | 81          | DSAEK Precut     | Uncut for all cases | Candida glabrata (aqueous tap donor lenticule) | 28                            | Positive for all cases | na for all cases | Same procedure for all patients. PK-intraocular amphotericin B, amikacin, vancomycin, cefazolin | | | 20/100                  | No |
|                  | 67           | 67          | DSAEK Precut     | Uncut for all cases | Candida glabrata (aqueous tap)        | 28                            | Positive for all cases | na for all cases | Same procedure for all patients. PK-intraocular amphotericin B, amikacin, vancomycin, cefazolin | | | 20/100                  | No |

BSCVA, best spectacle corrected visual acuity; DSAEK, Descemet stripping automated endothelial keratoplasty; DMEK, Descemet membrane endothelial keratoplasty; PK, penetrating keratoplasty; HM, hand movement; NPL, no perception of light; RD, retinal detachment; na, not applicable; nr, not reported.
Microorganisms involved in the development of IIK are more commonly fungi, in the form of Candida spp and less frequently bacteria (tables 1 and 2). In both cases, the source of infection is primarily the donor cornea, with a high correspondence between the organisms isolated from the corneoscleral rims and the ones identified in the recipients postoperatively. Regardless of the type of lamellar keratoplasty, early signs of infection may be noticed in the form of deep stromal infiltrates developing on average 1 month after surgery (tables 1 and 2). Onset of infection may occur as early as few days and up to 3 months after surgery, depending on the pathogenicity, microbial load and virulence of the infectious agent. A high index of suspicion is required to diagnose IIK, as it often presents with minimal inflammatory signs and symptoms. At onset, slight ocular pain and redness may be the only symptoms reported by patients, while visual acuity may be unaffected. At slit lamp examination, the cornea is usually clear, single or multiple whitish infiltrates, ranging from less than 0.5–2 mm in diameter, located at the graft–host interface, are the only visible signs of infection (figure 1). The anterior chamber is usually quiet with no inflammation. Anterior segment optical coherence tomography is helpful to confirm the location of the infiltrates at the graft–host interface (figure 2), but does not offer diagnostic hints of the causative agent. In vivo confocal microscopy can be useful in cases where Candida spp infection is suspected by detecting hyperreflective round budding-like structures with a granular appearance, measuring 2–4 µm, with the absence of hyphae-like structures. Nonetheless, the sensitivity and specificity of this examination are highly dependent on operator experience, and its diagnostic capability is yet to be confirmed in the setting of IIK.

Worsening of the infection is characterised by coalescence of the infiltrates that increase in size and assume less-defined margins, with oedema and infiltration of the overlying stroma. The anterior chamber may show reaction with cells and seldomly hypopyon (figure 3). At this point, ocular pain and photophobia are markedly increased and visual acuity is reduced from previous visits. Hsu et al. reported a case of Candida albicans interface infection after DSAEK rapidly developing corneal perforation and endophthalmitis few days after surgery.

Due to the initial asymptomatic clinical picture and the similarity to epithelial ingrowth, IIK diagnosis and treatment are often postponed until symptoms and signs of spreading of the infection become evident. Early warning of a possible risk of infection may come from donor rim cultures that can address identification and drug sensitivities of the potential infectious microorganism within few days after surgery. This information is particularly useful in the event of an interface infection due to inherent difficulty to obtain microbiological samples, without surgical intervention and to the high correspondence between microorganisms isolated from recipient specimens and the ones cultured from donor rims (tables 1 and 2). This may hold true particularly when donor rims are infected by Candida species where the risk of contamination of the donor mate cornea has also to be taken into account. In our literature review, positive donor rim cultures were highly predictive of the infectious agents isolated from recipients, not only for the majority of fungal but also for the minority of bacterial isolates. Candida species was the isolate most commonly involved in the development of interface keratitis after both DALK and EK (DSAEK and DMEK), suggesting a possible predisposition of this microorganisms for growing in...
a sequestered hypoxic environment, protected from the host immune system response.

Therapeutic algorithms for IIK are not yet defined. Conventional approach to the diagnosis and treatment of microbial keratitis is not applicable to IIK due to the deep stromal location of the infiltrates that precludes access for scrapings and cultures and impedes topical drug penetrations. Kitzman et al described a case of IIK after DSAEK, caused by C. albicans, with an unusual extension to the corneal surface, allowing for scraping and cultures, that was successfully treated with topical antifungals. On the basis of the clinical appearance and of the available information (donor rim culture), treatment is usually started empirically with broad spectrum antifungal drops including antifungals (amphotericin B 0.15% or voriconazole 1%) and, in cases of highly suspected or proved fungal infection, with systemic antifungals (oral voriconazole 100–200 mg two times a day or oral fluconazole 200 mg two times a day) in several cases with the dual purpose of reducing the microbial load and provide ample material for microbiology in order to address postoperative treatment. Disadvantage of this procedure is the risk of disseminating the infection into the anterior chamber and causing endophthalmitis. For this reason, donor lenticule removal was often followed by multiple intracameral and/or intravitreal injection of antifungals with a possible risk of toxicity for the intraocular structures. In our review, five patients (16%) with IIK after DALK developed endophthalmitis requiring combined PK and pars plana vitrectomy. Among these, three were initially treated by donor lenticule removal. To the contrary, none of the patients with IIK after DALK developed endophthalmitis, but donor graft exchange, attempted in three cases, was successful only in one. Collected data suggests that in DALK, the host DM is temporary capable to withhold the infection and avoid dissemination, explaining the better visual outcomes and the fewer complication recorded after excisional PK in patients with DALK compared with patients with EK.

Early excisional PK with removal of the sequestered infection may be advocated as a safe and effective measure to treat a post-LK infection of fungal origin. In a large series of IIK cases after DSAEK, Nahum et al described the results of early excisional PK with intracameral antimonials injection at the end of surgery. None of these patients developed endophthalmitis and most patients retained good visual acuity and a long-term graft clarity. Because the procedure was conducted in relatively quiet eyes, postoperative complications (ie, recurrence of infection, graft failure, macular oedema, glaucoma), frequently developing after longstanding inflammation, were few.

In conclusion, any small whitish interface opacity occurring days to weeks after any kind of PK should be followed closely and considered infectious, especially in the setting of a positive rim culture. Whenever we suspect a IIK, fungal infection by Candida species, originating from the donor graft, has to be considered the most likely diagnosis. Donor rim cultures of the grafted cornea as well as the mate cornea should be traced with the help of the eye bank to gather clues of the possible infectious agent. Medical treatment with direct injection of antifungals in the graft–host interface can be attempted to spare further surgical intervention. In view of the endophthalmitis risk, early intervention with excisional PK should be considered whenever signs of spreading of the infection become evident despite treatment.

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REFERENCES

1 Tan DT, Dart JK, Holland EJ, et al. Corneal transplantation. Lancet 2012;379:1749–61.
2 Kymionis GD, Mikropoulos DG, Portaliou DM, et al. New perspectives on lamellar keratoplasty. Adv Ther 2014;31:494–511.
3 Arenas E, Esquenazi S, Anwar M, et al. Lamellar corneal transplantation. Surv Ophthalmol 2012;57:510–29.
4 Tsai E, Fogel E, Hansen K, et al. Candida interface infections after descemet stripping automated endothelial keratoplasty. Cornea 2016;35:456–64.
5 Pand A, Pushnik N, Nainiwal S, et al. Rhodotorula sp. Infection in corneal interface following lamellar keratoplasty—a case report. Acta Ophthalmol Scand 1999;77:227–8.
6 Fontana L, Parente G, Di Pede B, et al. Candida albicans interface infection after deep anterior lamellar keratoplasty. Cornea 2007;26:883–5.
7 Kanavi MR, Forouzan AR, Kamel MR, et al. Candida interface keratitis after deep anterior lamellar keratoplasty. Cornea 2007;26:913–6.
8 Zarei-Ghanavati S, Sedaghat MR, Ghavami-Shahri A. Acute Klebsiella pneumoniae interface keratitis after deep anterior lamellar keratoplasty. Jpn J Ophthalmol 2011;55:74–6.
9 Catteri L, Babighian S, Rapizzi E, et al. Fungal keratitis following deep lamellar keratoplasty. Semin Ophthalmol 2011;26:33–5.
10 Bahadir AE, Bozkurt TK, Kutan SA, et al. Candida interface keratitis following deep anterior lamellar keratoplasty. Int Ophthalmol 2012;32:383–6.
11 Sedaghat MR, Hosseinpoor SS. Candida albicans interface infection after deep anterior lamellar keratoplasty. Indian J Ophthalmol 2012;60:328–30.
12 Wessel JM, Bachmann BO, Meiller R, et al. Fungal keratitis following Candida albicans interface infection after deep anterior lamellar keratoplasty. Case Rep Child Med 2013;2013.140435.
13 Murthy S, Jain R, Swarup R, et al. Recurrent non-tuberculous mycobacterial keratitis after deep anterior lamellar keratoplasty. BMJ Case Rep 2013;2013:bcr201300641.
14 Le Q, Wu D, Li Y, et al. Early-onset Candida glabrata interface keratitis after deep anterior lamellar keratoplasty. Optom Vis Sci 2015;92:e93–6.
15 Kodavoor SK, Dandapani R, Kausch AR. Interface infectious keratitis following deep anterior lamellar keratoplasty. Indian J Ophthalmol 2016;64:597–600.
16 Koenig SB, Wirostko WJ, Fish RI, et al. Candida keratitis after descemet stripping and automated endothelial keratoplasty. Cornea 2009;28:471–3.
17 Kitzmann AN, Wagoner MD, Syed NA, et al. Donor-related candida keratitis after descemect stripping automated endothelial keratoplasty. Cornea 2009;28:825–8.
18 Chew AC, Mehta JS, Li L, et al. Fungal endophthalmitis after descemect stripping automated endothelial keratoplasty—a case report. Cornea 2010;29:346–9.
Review

19 Lee WB, Foster JB, Kozarsky AM, et al. Interface fungal keratitis after endothelial keratoplasty: a clinicopathological report. *Ophthamtic Surg Lasers Imaging* 2011;42:e44–8.

20 Ortiz-Gomariz A, Higuera-Esteban A, Gutiérrez-Ortega ÁR, et al. Late-onset candida keratitis after descemet stripping automated endothelial keratoplasty: clinical and confocal microscopic report. *Eur J Ophthalmol* 2011;21:498–502.

21 Sharma N, Agarwal PC, Kumar CS, et al. Microbial keratitis after descemet stripping automated endothelial keratoplasty. *Eye Contact Lens* 2011;37:320–2.

22 Yamazoe K, Den S, Yamaguchi T, et al. Severe donor–related candida keratitis after descemet’s stripping automated endothelial keratoplasty. *Graefes Arch Clin Exp Ophthalmol* 2011;249:1579–82.

23 Holz HA, Pirouzian A, Sudesh S, et al. Simultaneous interface candida keratitis in 2 hosts following descemet stripping endothelial keratoplasty with tissue harvested from a single contaminated donor and review of clinical literature. *Asia Pac J Ophthalmol* 2012;1:162–5.

24 Tu EY, Hou J. Intrastromal antifungal injection with secondary lamellar interface infusion for late-onset infectious keratitis after DSAEK. *Cornea* 2014;33:990–3.

25 Nahum Y, Russo C, Madi S, et al. Interface infection after descemet stripping automated endothelial keratoplasty: outcomes of therapeutic keratoplasty. *Cornea* 2014;33:893–8.

26 Weng C, Parke DW, Walter SD, et al. Candida glabrata endophthalmitis transmitted from graft to host after descemet stripping automated endothelial keratoplasty. *JAMA Ophthalmol* 2014;132:1381–3.

27 Hsu YJ, Huang JS, Tsai JH, et al. Early–onset severe donor-related candida keratitis after descemet stripping automated endothelial keratoplasty. *J Formos Med Assoc* 2014;113:874–6.

28 Villarubia A, Cano-Ortiz A. Candida keratitis after descemet stripping with automated endothelial keratoplasty. *Eur J Ophthalmol* 2014;24:964–7.

29 Wilde C, Messina M, Mosini T, et al. Interface scopulariopsis gracilis fungal keratitis following Descemet’s Stripping Automated Endothelial Keratoplasty (DSAEK) with a contaminated graft. *Int Ophthalmol* 2018;38:2211–7.

30 Thompson M, Carli D. First reported case of donor related candida endophthalmitis after descemet membrane endothelial keratoplasty. *Open Ophthalmol J* 2017;11:117–21.

31 Tu EY, Majmudar PA. Adjuvant stromal amphotericin B injection for late-onset DMEK infection. *Cornea* 2017;36:1556–8.

32 Porter AJ, Lee GA, Whitehead K. Infectious crystalline keratopathy after descemetas stripping endothelial keratoplasty. *BMJ Case Rep* 2017;2017:bcr-2017-220464.

33 Paloua S, Sivaranan K, Joag M, et al. Candida endophthalmitis after descemet stripping automated endothelial keratoplasty with grafts from both eyes of a donor with possible systemic candidiasis. *Cornea* 2018;37:515–8.

34 Aldave AJ, DeMatteo J, Glasser DB, et al. Report of the eye bank association of America medical advisory board subcommittee on fungal infection after corneal transplantation. *Cornea* 2013;32:149–54.

35 Rauen MP, Goins KM, Sutphin JE, et al. Impact of eye bank lamellar tissue cutting for endothelial keratoplasty on bacterial and fungal corneoscleral donor rim cultures after corneal transplantation. *Cornea* 2012;31:376–9.

36 Brothers KM, Shanks RMQ, Hurlbert S, et al. Association between fungal contamination and eye bank–prepared endothelial keratoplasty tissue. *JAMA Ophthalmol* 2017;135:1184–90.

37 Ritterband DC, Shah MK, Meskin SW, et al. Efficacy and safety of voriconazole as an additive in optisol GS: a preservation medium for corneal donor tissue. *Cornea* 2007;26:343–7.

38 Fontana L, Eranni PG, Zerbini A, et al. Frequency of positive donor rim cultures after penetrating keratoplasty using hypothermic and organ–cultured donor corneas. *Cornea* 2007;26:552–6.

39 Hau SC, Dart JK, Vesaluoma M, et al. Diagnostic accuracy of microbial keratitis with in vivo scanning laser confocal microscopy. *Br J Ophthalmol* 2010;94:982–7.

40 Das S, Samant M, Garg P, et al. Role of confocal microscopy in deep fungal keratitis. *Cornea* 2009;28:11–13.

Fontana L, et al. *Br J Ophthalmol* 2019;103:307–314. doi:10.1136/bjophthalmol-2018-312938