Infezioni trasmesse dal limbo di cheratoplastica dopo il trapianto

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Infections following keratoplasties

1) Keratititis

- Infiltrates (superficial, deep), all keratoplasties

- Interface infectious keratitis, DALK and EK

2) Endophthalmitis, PK and EK, rare following DALK

Infections following keratoplasties

Incidence rates of infections following keratoplasty:

- 1.7 – 7.4% in developed countries
- 11.9 in developing world

Host-related problems, persistent epithelial defects and loose sutures, the major risk factor

Vajpayee et al. Major review Survey Opthhalmol 2007

Endophthalmitis USA 0.42% incidence/18.083 corneal transplants

0.12% incidence/2.261.779 cataract surgery

Du et al. Opthhalmology 2014

UK 0.67% after PK

Chen et al. Opthhalmology 2015

Eye Bank Association of America Adverse Reaction Report 2007-2014

354.930 corneal grafts (24.482 PK/year; 20.570 EK/year; 940 DALK/year)

99 (0,02%) **endophthalmitis** (mean 12 cases/year; 2,8 per 10.000)

61% EK, 37% PK

increasing trend (total 5 in 2007, 26 in 2013)

(fungal 2 in 2007, 16 in 2013)

66 (0,01%) **keratitis** (mean 8 cases/year; 1.8 per 10.000)

67% EK, 29% PK

increasing trend (total 3 in 2007, 19 in 2013)

(fungal 2 in 2007, 13 in 2013)

Edelstein et al. Cornea 2016

Fungal infections after corneal transplantation

- 221.391 distributed corneas 2007-2010
- 31 culture-proven infections (14 keratitis, 17 endophthalmitis)
- 0.022% EK vs 0.012% PK (P= 0.076)
- No association between lamellar tissue prepared by the surgeon or by the eye bank
- Increasing trend in the incidence of fungal infections, not statistically significant.
- Candida species (albicans, glabrata, tropicalis, dubliniensis) the only fungi identified
- **The other cornea from the same donor very likely transmits the infection**

Aldave et al. Report EBAA Cornea 2013

Infections related to contaminated donor tissues

- Systematic literature review of penetrating keratoplasty with reported microbiological investigation of donor corneoscleral donor rim after refrigerated storage (1975-2006)

17.614	corneal grafts (PK)
2.459 (14.0%)	positive donor rim culture
30 (0.17%)	laboratory-confirmed endophalmitis within 3 months
70%	concordant recipient and donor isolates
100%	concordant with Candida (10 eyes)
55%	concordant with bacteria (11 eyes)

Wilhelmus and Hassan Ophthalmology 2007

Prognostic role of donor cornea rim cultures

- Endophthalmitis risk among eyes receiving a cornea **with culture-positive rim**

  12.2 times greater than those with culture-negative

- The odds of **fungal** endophthalmitis

  247 times greater

Wilhelmus and Hassan Ophthalmology 2007

Conclusions

Endophthalmitis is an uncommon (0.1-0.2%) but serious complication

Endophthalmitis is more likely with culture-positive donor cornea

but infections occur much less often than donor microbial contamination

The value of routinely submitting donor rims for culture

- cost US 2.000.000 – 6.000.000 per year
- prognostic value modest: risk of endophthalmitis 0.2% → 1% with positive culture

The performance of donor rim cultures has an uncertain role in prevention of

infections, however

the high positive likelihood ratio suggest that fungal cultures may be worthwhile

Wilhelmus and Hassan Ophthalmology 2007

Incidence of fungal infections after EK hypothermic storage vs organ culture

- 10 cases 2014-1017 in hypothermic medium, 3 European centres, 9 Candida, 3 pairs of mate corneas caused infections in 6 recipients
- 16.862 corneas for EK, 16 European Eye Banks 2012-2017

  →14.476 organ culture / 2.386 hypothermic solution

  →17 infections (0.1%)
  - 15 (82%) fungal, 14 Candida spp.
  - 3/14.476 (0.02%) organ culture
  - 14/2.386 (0.50%) hypothermic storage ($p<0.0001$)

Lau et al. Br J Ophthalmol 2018

Conclusions

1) **Increased risk for Candida** infections following EK

2) Increased risk when the tissue has been stored **in hypothermic medium** compared with organ culture

3) Plausible explanation

i) addition of an antifungal in organ culture (amphotericin B)

ii) growth of a fungi is facilitated at 34° →contamination identified, and tissue discarded

4) Advantage to add antifungal in hypothermic medium? Identification of contaminants before tissue release?

Lau et al. Br J Ophthalmol 2018

Interface infectious keratitis-DALK

42 cases 12 DALK, 31 EK (search 1949-2018)

DALK Candida 7/12 (63%), Klebsiella, Rhodotolura, Mycobacterium

donor rim culture in 5 cases: 2 cases negative, 3 positive

Onset: 29 days (2-120)

Treatment: PK 9/12

None developed endophthalmitis

Fontana et al. Review Br J Opthalmol 2018

Interface infectious keratitis - EK

42 cases 12 DALK, 31 EK (search 1949-2018)

EK 29 DSAEK, 2 DMEK

Candida 21/42 (75%), Aspergillus 1, bacteria 5, Nocardia 1

donor rim culture in 28 cases: 13 cases negative, 15 positive (all Candida)

Onset: 28 days (1-120)

Treatment: medical success in only 1 case

5 developed endophthalmitis

3 severe sight loss

Fontana et al. Br J Opthalmol 2018

Conclusions

- Overall perception of an increased risk of fungal infection after EK may be the consequence of over-reporting a novel complication after a new surgical procedure
- Tissue manipulation either in the eye bank or in the operating room does not seem to influence the risk of infections
- The donor -not the processing- seems to be the source of infection
- Candida: most common microorganism

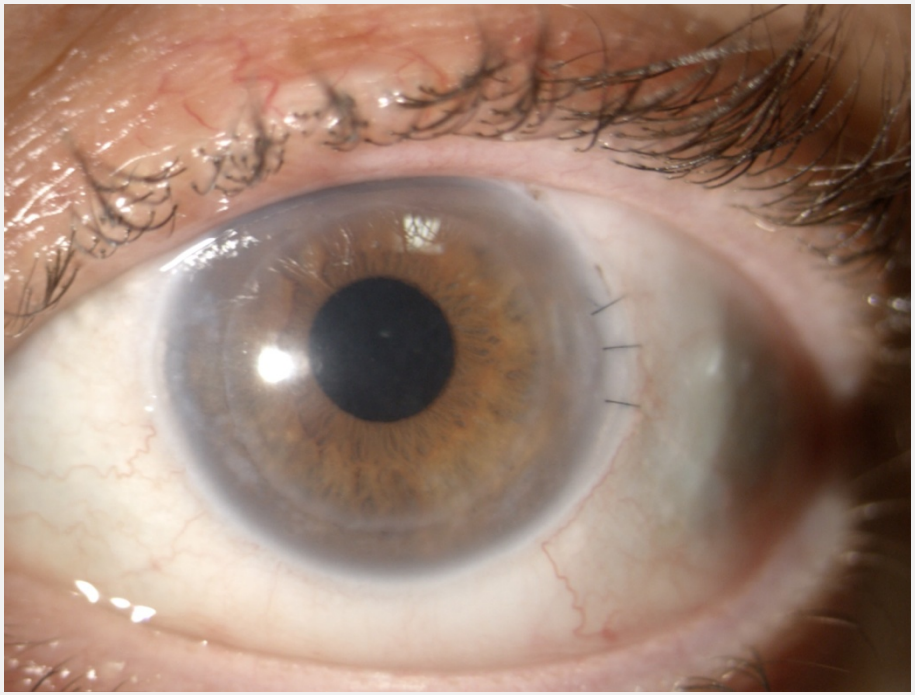
Fontana et al. Br J Ophthlmol 2018

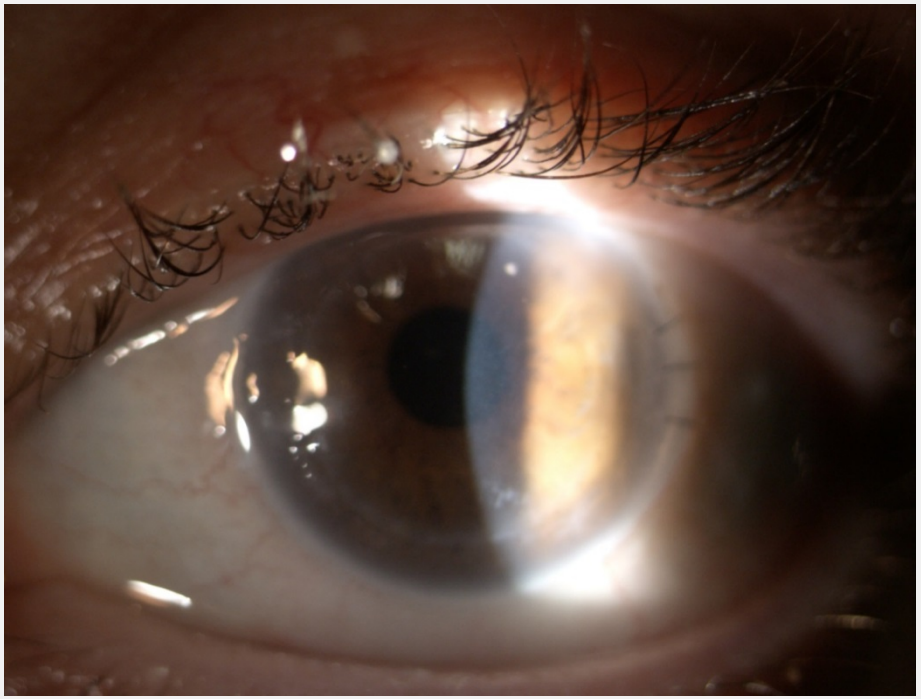
Conclusions (cont'd)

- Onset: few days – 3 months
- Initial asymptomatic clinical picture and similarity to epithelial ingrowth

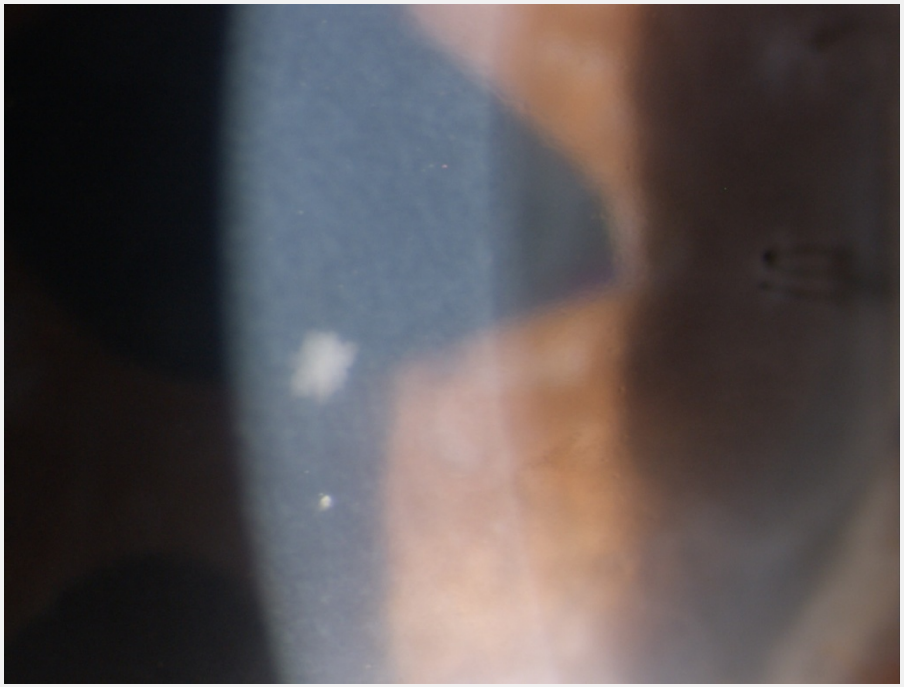
Fontana et al. Br J Ophthlmol 2018

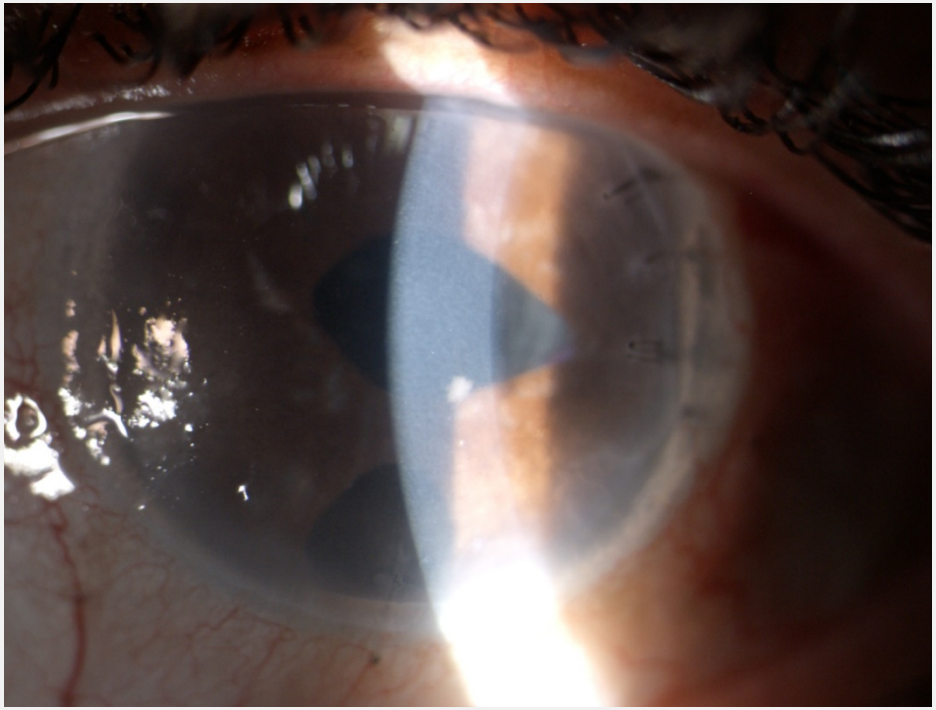
One month after DSAEK



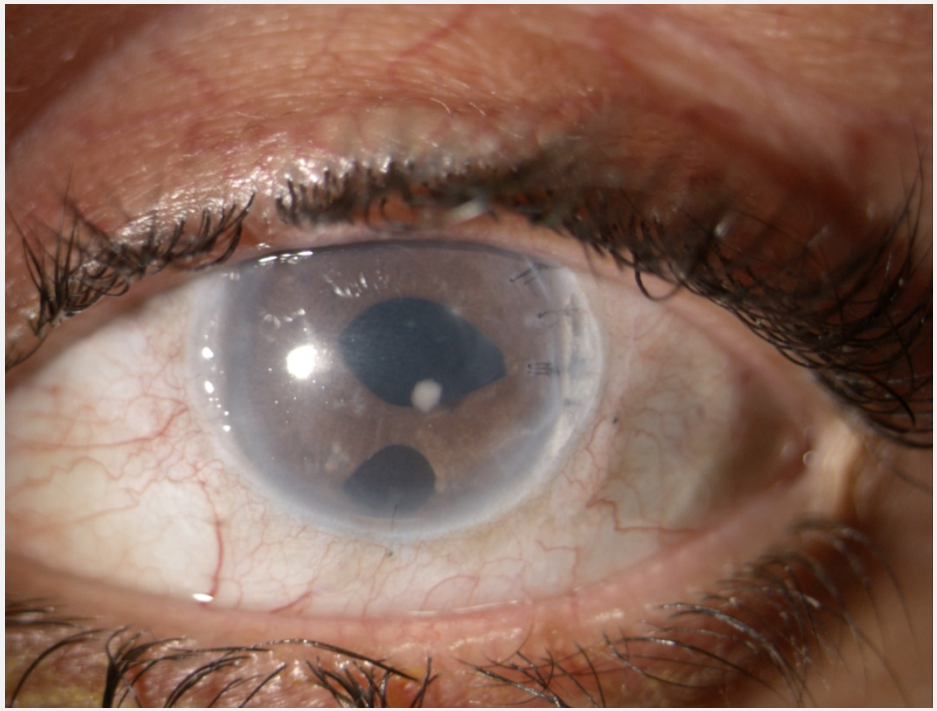


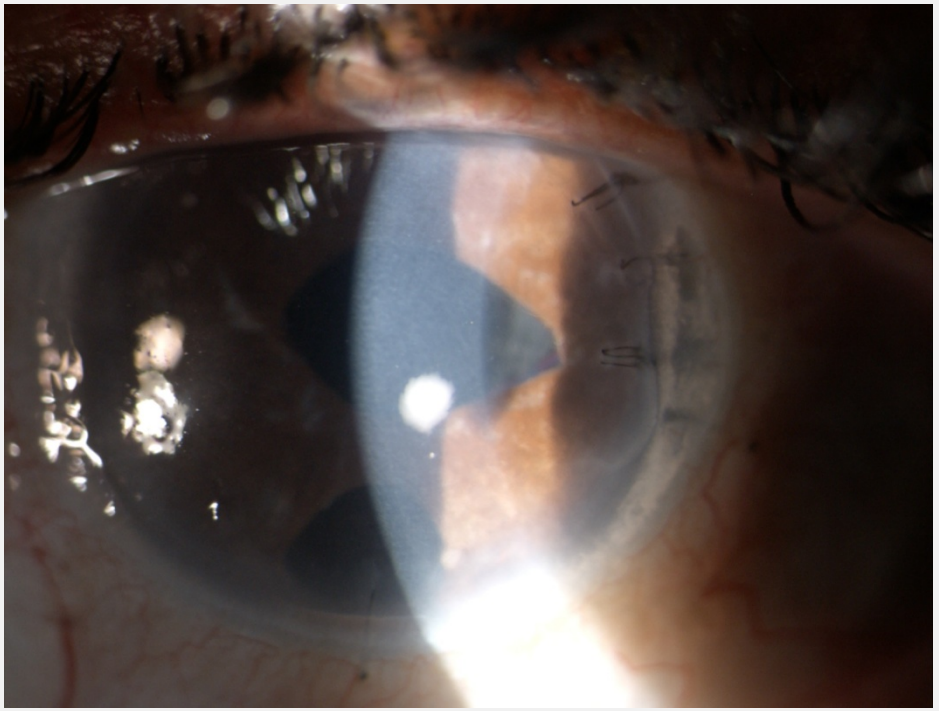
Two months after DSAEK





One month later





Conclusions

- Onset: few days – 3 months
- Initial asymptomatic clinical picture and similarity to epithelial ingrowth
- Early warning may come from donor rim culture
- In vivo confocal microscopy can be useful
- In case of infection, early excisional PK is a safe and effective measure

Fontana et al. Br J Ophthlmol 2018

Infections rates for eye bank-prepared and non-eye bank-prepared grafts for EK

- 17.035 corneas 2006-2017, single American eye bank
  - 44% prepared by surgeons
  - 82 reported infections
    - 11 with eye bank-prepared grafts
    - 42 with non-eye bank-prepared grafts

  Tissue-related infections were higher in non-eye bank prepared grafts

Mathes et al. Cornea 2018

Clinical onset

Endophthalmitis

- -14 days (1-221)
- -bacterial 2,5 days
- -fungal 33 days

Keratitis

- -29 days (1-216)
- -bacterial 6 days (1-125)
- -fungal 45 days (3-216)

Edelstein et al. Cornea 2016

Transmission of herpes simplex virus-1

Many studies describe long-term viral presence in the cornea

It does appear that HSV-1 may either develop latency in the cornea (limbal stem cells, keratocytes, or endothelium) or persist in a low-replicative state

Several reports of primary graft failure due to HSV that may represent donor-host transmission through corneal transplantation

Farooq and Shukla Future Virol 2011

Transmission of herpes simplex virus-1

In 2001 a case was published in the Lancet, HSV from the donor was identical to that found in the recipient with PCR-based DNA fingerprint

Remeijer et al. Lancet 2001

However, in most reported cases there was no definitive evidence that the donor rather than the recipient was the source of virus

A study detected HSV DNA in 3/80 samples of donor culture medium but it did not lead to ocular disease in the recipient

Morris et al. Br J Ophthalmol 1996

Conclusions

The significance of HSV-1 presence in donor corneas remains unknown

It is possible that long-term presence in the cornea is a sign of no-neuronal latency, and that the virus could reactivate after transplantation causing primary graft endothelial failure

Whether the risk of transmitting HSV-1 will influence eye banking standards remains to be seen

Farooq and Shukla Future Virol 2011

Conclusions and suggestions

- Infections related to contaminated donor tissue are uncommon but serious complication
- Published data dependent on voluntary reporting on surgeons: infections might be underestimated
- Trend of increasing positive fungal rim cultures between 2011 and 2015 (P= 0.058)

Conclusions and suggestions

- Endophthalmitis risk among eyes receiving a cornea with culture-positive rim, **247 times greater for fungi**

  → donor rim fungal culture is worthwhile

- Candida the most common microorganism
- Tissue manipulation either in the eye bank or in the operating room does not seem to influence the risk of infections
- Organ culture is safer than hypothermic storage
- Importance of reporting positive rim cultures to the Eye Bank (fellow donor cornea)

Conclusions and suggestions

- In case of positive donor rim culture

  prophylactic therapy 7-fold reduction in the post-op infections

  recommendation of topical and systemic prophylactic antifungal

  treatment for three months

Onset: few days – 3 months

  initial asymptomatic clinical picture and similarity to epithelial ingrowth

- In vivo confocal microscopy can be useful

- In case of infection, early excisional PK is a safe and effective measure

Thank you