

Post-keratoplasty infections  
related to  
contaminated donor tissues

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# Infections following keratoplasties

## 1) Keratitis

- 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 Ophthalmol 2007

Endophthalmitis USA 0.42% incidence 18.083 corneal transplants

0.12% incidence 2.261.779 cataract surgery

Du et al. Ophthalmology 2014

UK 0.67% after PK

Chen et al. Ophthalmology 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%)	<b>endophthalmitis</b> (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%)	<b>keratitis</b> (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)

# 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, no statistically significant.

Candida species (albicans, glabrata, tropicalis, dubliniensis) the only fungi identified

The other cornea from the same donor very likely transmits the infection

# 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 endophthalmitis within 3 months
70%	concordant recipient and donor isolates
100%	concordant with Candida (10 eyes)
55%	concordant with bacteria (11 eyes)

# 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



# Incidence of fungal infections after EK hypothermic storage vs organ culture

10 cases 2014-2017 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 ( $p < 0.0001$ )

# 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 fungal contaminant is facilitated at 34° ,  
contamination identified, and tissue discarded
- 4) Further research to explore the advantage to add antifungal in hypothermic medium and possibility to identify contaminants before tissue release

# Interface infectious keratitis

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

# Interface infectious keratitis

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 Ophthalmol 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 and not the processing seem to be the source of infection

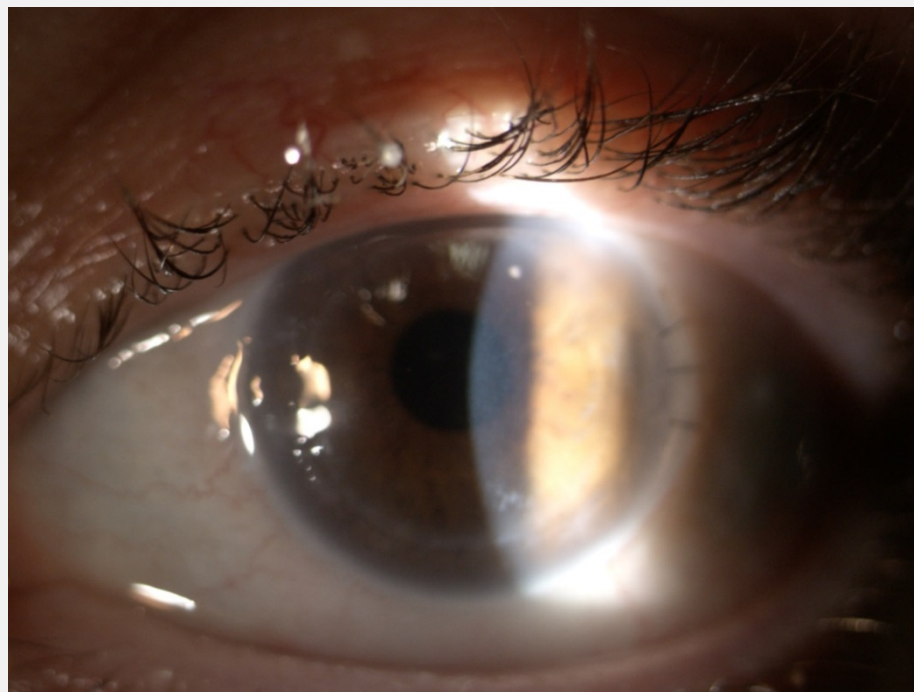
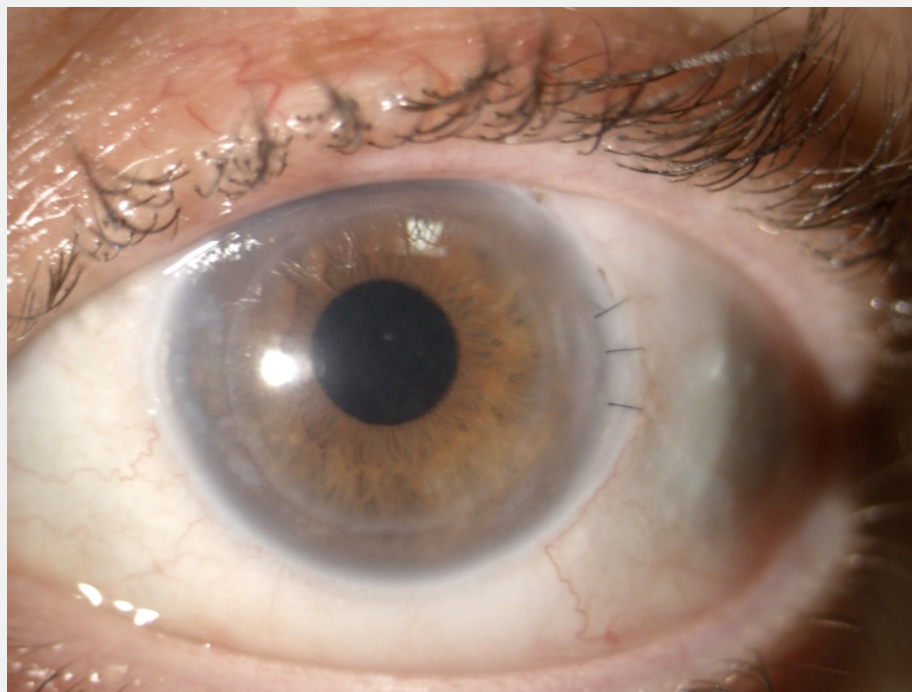
Candida the most common microorganism

# Conclusions

Onset: few days – 3 months

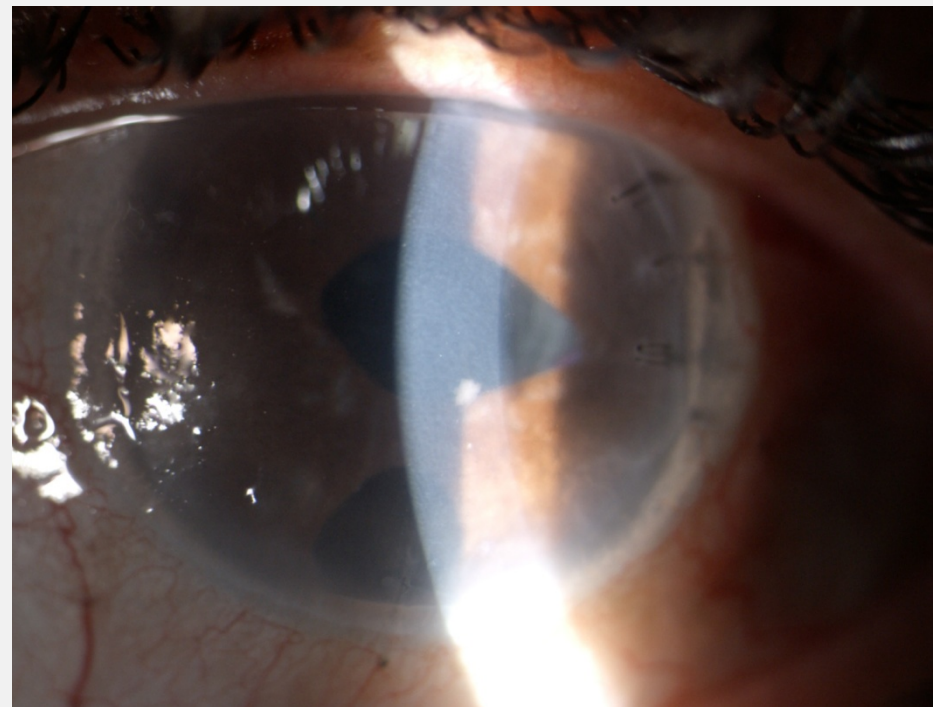
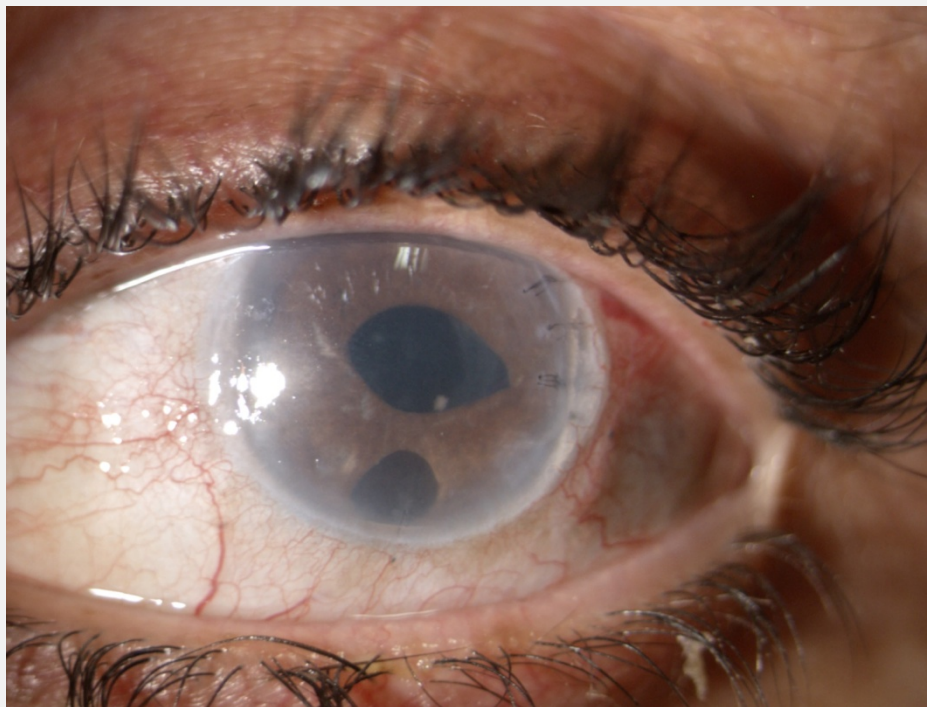
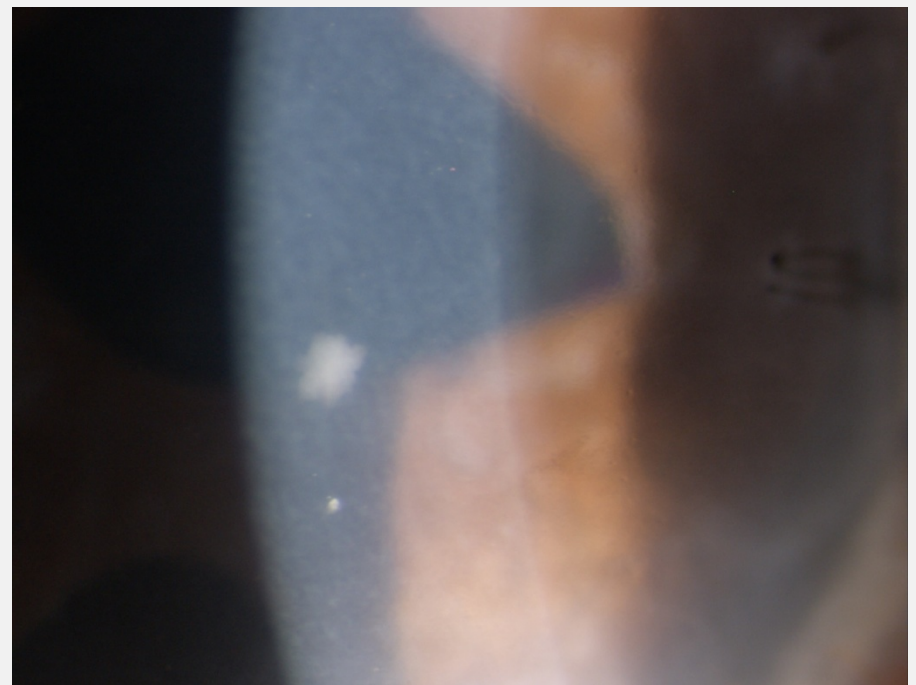
Initial asymptomatic clinical picture and similarity to epithelial ingrowth

One month after DSAEK



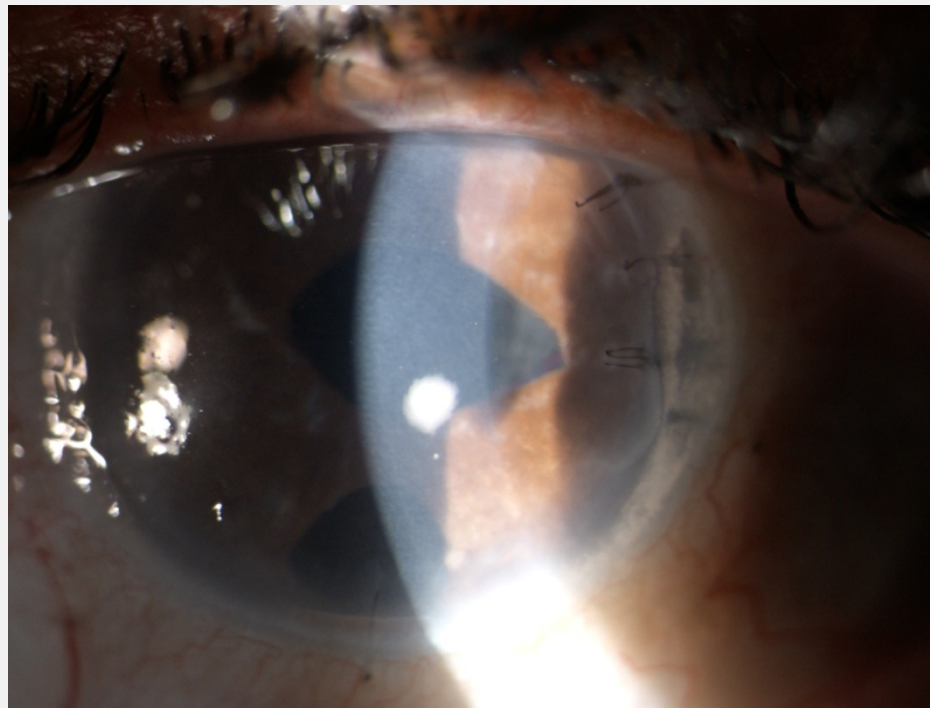


Two months after DSAEK





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

# 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*

## 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)

# 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

# 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**