The Investigation Process Following a Cluster of Post Descemet Stripping Automated Endothelial-Keratoplasty (DSAEK) Endophthalmitis at a Single Eye Bank in Pre-prepared Corneal Tissue

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ABSTRACT

Purpose: To describe a cluster of endophthalmitis cases following Descemet Stripping Automated Endothelial Keratoplasty (DSAEK) procedures using pre-cut corneal donor tissue from a single eye bank across a four-month period.

Methods: case series and procedural review

Results: 5 eyes of 5 patients were diagnosed with endophthalmitis between 1 day and 2 weeks following DSAEK surgery. *Candida parapsilosis* was identified as the causative organism in all cases. Microbiological investigation revealed 3 cases (inclusive of 2 eyes from the same donor) exhibited an identical strain indicating probable contamination. Contamination of the microkeratome head was considered the probable reason however the true source could not be confirmed. Two further cases were diagnosed as non-identical strains suggesting additional sources.

Conclusion: The appearance of a cluster requires immediate attention to identify potential sources and minimise further risk. Review of the preparation process is discussed.

Key Words: cornea; donation; Eye Bank; endophthalmitis

As the incidence of post-keratoplasty infection remains low, the presence of several cases in close succession demands urgent investigation.[1-3] Outbreak management and containment, epidemiological investigation and clear communication with relevant authorities and stakeholders represent essential steps in the required review process.

A series of five cases of endophthalmitis following Descemet Stripping Automated Endothelial Keratoplasty (DSAEK) procedures using pre-cut corneal donor tissue and organ culture storage techniques from a single eye bank occurred across a four month period from April to August 2017. We describe the case series and following response undertaken and provide a working investigative and administrative example for future reference.

CASE SERIES

Two corneas from a single donor (donor 2, in order of retrieval) were prepared (pre-cut) at the Lions New South Wales Eye Bank (LNSWEB) in late April 2017 for transplant the following day. As per protocol at the time, a different microkeratome and blade were used for each eye however the handpiece was wiped between procedures. Notification was received by LNSWEB the afternoon of the day of surgery that the microbiological samples from the transport media were positive for an organism, later identified as *Candida parapsilosis*. The donor corneal tissue had been stored for 19 days prior to transport preparation.

The operating surgeons were immediately notified.

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The procedure for recipient 1 (in order of infection presentation) had been completed however the procedure for recipient 2 was still underway albeit the cornea implanted. Recipient 2 had the cornea removed immediately. Both patients were symptomatic of endophthalmitis from day one post-surgery and were subsequently found to be positive for *Candida parapsilosis following culture*. Both patients had undertaken the lamellar graft procedures at separate private hospitals. Recipient 1 underwent a secondary graft replacement procedure at day 2.

Six weeks after the first notification, the LNSWEB was contacted regarding a further case of endophthalmitis (recipient 3) at eight weeks post-transplant of pre-cut DSAEK (donor 1 – prepared 5 days before donor 2). This surgical procedure was performed for endothelial failure secondary to multiple glaucoma procedures. Fungal and bacterial investigation confirmed *Candida parapsilosis* as the causative organism. The transport media micro sample was negative.

Recipient 4 was reported two days after recipient 3. This patient had undergone a DSAEK procedure for prior graft failure and presented with signs of endophthalmitis six weeks after surgery. The causative organism was again *Candida parapsilosis*. The tissue for this procedure (donor 3) had been prepared the same day, but after the tissue from donor 2. The transport media micro sample was negative for this cornea and the surgery was undertaken at a different public hospital.

Eleven weeks following the prior case, the LNSWEB was notified of the final case of suspected endophthalmitis (recipient 5). Presenting fifteen weeks after receiving a pre-cut donor cornea (donor 4) for treatment of Fuchs Dystrophy, this recipient was confirmed as having an infection caused by *Candida parapsilosis*. The transport media micro sample was negative; surgery was undertaken at the same public hospital as recipient 3 but six days later; the donor 4 tissue was prepared for DSAEK two weeks after that of donor 3, and there had been seven other DSAEK grafts from four donors transplanted in-between without incident.

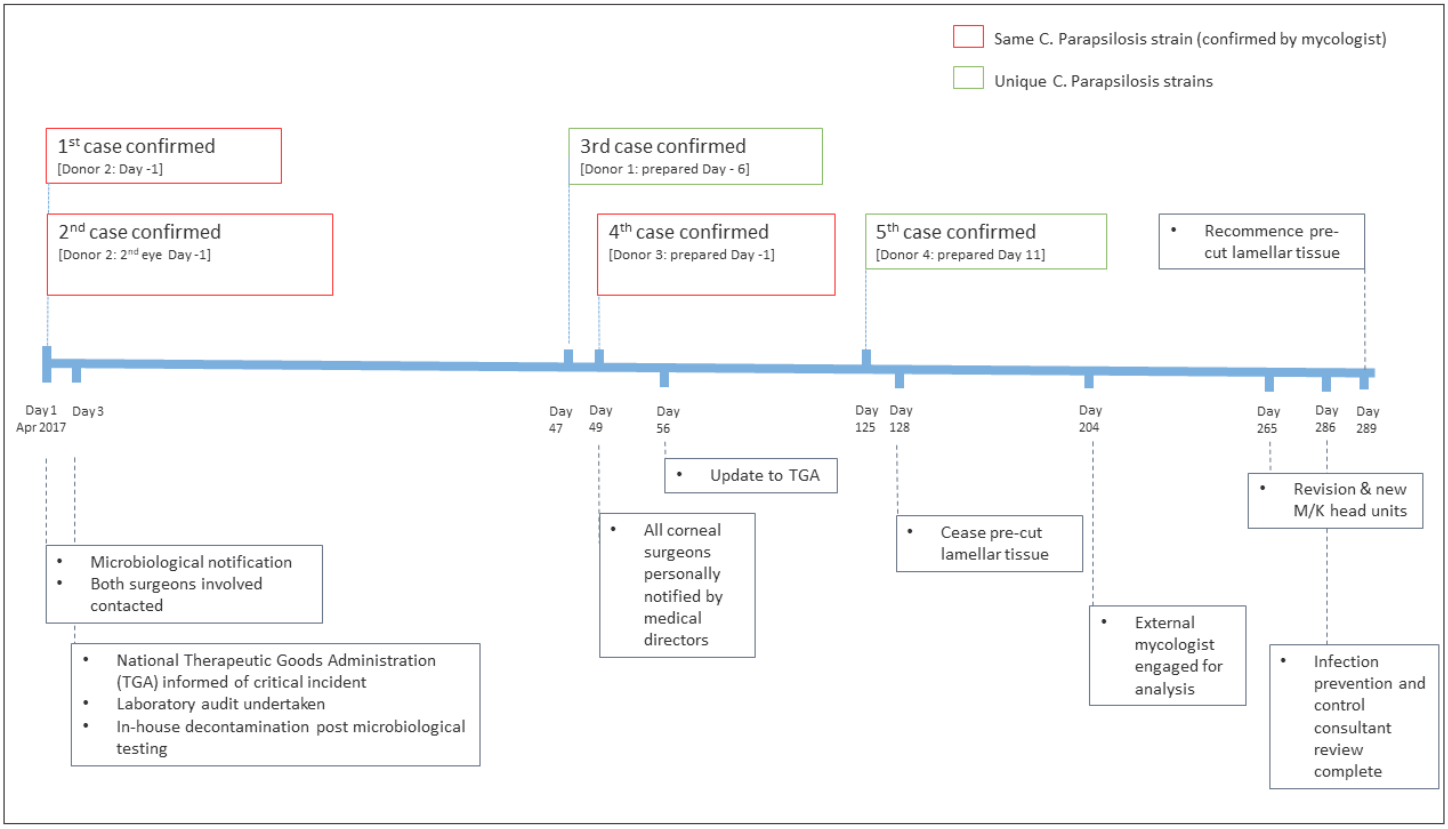

Figure 1: *Episode timeline*

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ACTION COURSE

Following confirmation of the initial two cases, the Therapeutic Goods Administration (TGA), the regulatory authority for tissue banking in Australia, was informed of the critical incident and an internal review of the laboratory and work environment was undertaken. The Laminar flow cabinet and microkeratomes underwent additional in-house decontamination after microbiological testing. No growth was found on the microkeratome console or handpiece swabs. The hospital scientists underwent microbial assessment to ascertain the possibility of local infection. One hand of one hospital scientist identified scant skin flora above routine levels (*Staphylococcus aureus*). Weekly environmental settle plates which had previously been performed routinely continued to show no abnormal growth.

Directly following the 4th case notification, all corneal surgeons that had received tissue from the LNSWEB over the previous three months were contacted directly by the Medical Directors to be made aware of the current findings and to remain alert for further possible cases of a likely cluster series.

Following the 5th case, the LNSWEB management team took the step to cease production of pre-cut lamellar tissue until further notification. The ensuing period involved a significant review of concurrent procedures. The TGA was informed of the additional cases and an external review committee was engaged to undertake an on-site inspection and external protocol review. This resulted in no irregular findings within either procedures or the laboratory setting. Identifying a common possible source represented an essential aspect of the investigation and subsequently an external mycologist (Centre for Infectious Diseases and Microbiology, Sydney) was engaged. This investigation found that the first, second (tissue from the same donor, number 2 in order of retrieval) and fourth cases represented an identical strain suggesting that the fourth case resulted from contamination derived from donor number 2. Although the other cases were identified as resulting from the same organism, these were identified as unique strains suggesting separate processes leading to the eventual clinical condition.

As all cases identified within the series involved pre-cut corneal tissue, this suggested that the microkeratome and or the cutting process represented a possible source of contamination. Of note, previous internal investigations had found no evidence of infective organisms within the microkeratome at any point. The review identified that the existing sterilisation protocol for the unit precluded sterilisation of the unit motors (in accordance with the manufacturers' guidelines). Consultation with the microkeratome production company confirmed no prior cases attributed to contamination through a motor head however the company subsequently provided an option for a microkeratome head unit which was autoclavable. The LNSWEB immediately replaced all current microkeratome heads with these sterilisable units.

Considering the review findings and the corresponding absence of subsequent cases of endophthalmitis during the six month period following cessation of pre-cut tissue, the re-introduction of tissue was tabled for discussion. An external infection prevention and control consultant was engaged to provide a final review of the investigation undertaken and the revision of practices. The consultant found that the review process undertaken by the tissue bank and the subsequent negative findings were satisfactory. The LNSWEB recommenced pre-cut lamellar tissue in February 2018. No further cases of contamination have been found in the 18 months following the re-introduction of pre-cut tissue.

DISCUSSION

Endophthalmitis following corneal transplantation is a rare but significant complication and continues to represent a concern for tissue bank staff and surgeons despite a relatively stable rate of infection over time.[1-3, 5-7] Factors including variable host immunity and increasing prevalence of fungi suggest that tissue banks, indeed all health care services, may require additional vigilance in the future.[8, 9]

Determining the primary source of infection as soon as possible is central to minimising the impact of any possible outbreak. Each case involved in our case series was prepared for DSAEK by the LNSWEB staff. This has precedence within the literature. Brothers et al found a significantly higher rate of infection in pre-cut tissue compared to unprocessed tissue.[6] The

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authors suggested that the increase in preparation time and the extended duration of tissue warming may have exacerbated the risk of microorganism formation. This study used Optisol-GS corneal, cold storage media. Faster microbial metabolism occurs at higher temperatures which may suggest that the use of organ-culture as a storage medium may be more appropriate than cold-storage solutions.[10] Organ culture medium represents our standard storage for donor tissue. Although pre-cutting the tissue represents an additional process to be conducted within the environment of the LNSWEB, it would be expected that this would not be clinically significant given the donor tissue has been maintained at room temperature and the medium contains anti-fungal additives. Further, an earlier study failed to find an association between fungal infection following endothelial keratoplasty and tissue prepared by either the surgeon or tissue bank technician suggesting other factors may contribute.[11] Wilde et al recently described three cases of fungal infection secondary to the dextran transport medium highlighting the possibility of post-cut contamination.[12]

The surgical procedure may represent an additional risk factor with wound dehiscence, suture-related complications and corneal venting incisions previously attributed to endophthalmitis following lamellar procedures.[13, 14] The lamellar interface has further been identified as a potential unique environment for microorganism proliferation as it remains sheltered from the eye's normal aqueous circulation and immune defence.[6] These concerns may represent a particular consideration in host patients with high fungal burden.[15, 16] Although a specific origin was not found across our series, identification of the fungal strains confirmed separate possible sources in three of the five cases supporting a significant review of both preparation and surgical processes.

With an affinity for frequent colonisation in health care settings and an ability to easily form a biofilm on prosthetic surfaces, *Candida parapsilosis* was the common thread in our series.[17,18] Of relevance, *C. parapsilosis* has been recognised previously as the most common species associated with eye infection.[19] Edelstein and co-authors have proposed that broad-spectrum antibiotics may be responsible for creating a non-competitive environment which supports increased fungal growth.[20] The long-term use of antibiotics and co-location within an intensive care unit suggested that the initial bilateral donor possibly represented a higher risk of increased fungal burden however this is in full hindsight.[21] Of practical importance, the presence of a fungal burden in one donor eye will more likely result in a fungal infection in the second recipient which was unfortunately born out in our second case.[10] Notification of a positive microbiological result in one eye of a bilateral donor therefore should nominally rule the second eye tissue from use. The adherent properties of the *C. parapsilosis* fungus likely resulted in the contamination of our 4th case which was prepared on the same day as the initial bilateral donor. This may have been expedited by the prior protocol which precluded sterilisation of the microkeratome head however it also suggests the increased virulence of the initial donor considering this had not occurred in over 300 prior pre-cut cases. Our eye bank subsequently exchanged microkeratome head units to allow sterilisation and no further cross-contamination has been identified in subsequent cases. Although this practice may be routine in many eye banks, it should be considered if not currently undertaken. Although all investigations during the process failed to confirm the presence of *C. parapsilosis* contamination within the laboratory environment, this remains a possibility. Of consideration, Koca et al highlight median survival times for various bacteria and fungi at between 26 to 30 days on various commonly worn fabrics suggesting an additional possible source albeit almost impossible to confirm.[22]

Practically, we believe that early and earnest communication with all relevant parties was an essential aspect of our process, both as an alert and to provide confidence that all measures were being assessed. The decision to temporarily halt pre-cut tissue as an option represented a further significant, but crucial step as a possible removal of the source origin. This was made following consultation with both LNSWEB management and operating surgeons.

This case series emphasizes the need for adherence to existing protocols albeit in the context of continuous review. We believe that the analysis and presentation of this series has provided important information for eye bank management that may minimise future outbreaks.

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***Table 1**: Recommendations following Eye Bank review*

Recommendation	Update/Outcome
1. Observe the recommended 3 month period of time before recommencement of cutting corneas.	The pre-cut cornea program was temporarily ceased in August 2017.
2. Purchase and install handpieces that can be sterilised and run validation process	The microkeratome used by LNSWEB was purchased in mid-2014. The LNSWEB was not aware that the manufacturer now produces a handpiece that can be sterilised until it contacted the company during the incident review. Handpieces x 4 were purchased arriving January 2018. To further reduce the risk of contamination, bilateral donor tissue is now prepared using separate instrumentation in addition to single use sterile consumables.
3. Validation trial of tissue pre-cut preparation using new equipment	A validation process was completed and the handpieces confirmed as being ready for use.
4. Apply additional process to standard operating procedures including tissue preparation prior to bioburden reduction and allowing additional time to allow for final micro results prior to releasing tissue for transplantation.	Routine rubbing of corneal surface prior to processing to remove loose epithelial cells and activate biofilms is to be undertaken. Epithelial tissue is removed to ensure optimal penetration of iodine during the preparation process. The addition of Chlorhexidine to the preparatory wash procedure has been discussed but not implemented at the time of submission. As the risk of additional bioburden remained minimal, the corneal tissue was occasionally released prior to secondary results becoming available. Following the case series, the introduction and testing of the transport media was brought forward to ensure that all samples are delivered for microbiology testing with sufficient time for at least 24 hours incubation prior to surgery. This has required consideration for the preparation staff and coordinators in providing tissue release times. Standard protocol: Organ Culture Storage Medium (OCS): batch sterility testing with confirmed sterility prior to availability. Organ Culture Transport Medium (OCT): Following the cell count in preparation for surgery use, the donor tissue is transferred to OCT. Six (6) hours post cell count an OCT sample is removed and sent for external microbiological testing. The tissue cannot be released
5. Review of incident by Therapeutic Goods Administration (National Regulatory Authority)	Conducted in November 2017 during on-site inspection by TGA. Note: there were no additional recommendations from this review.
6. Write up and publish / share with peers	The incident and findings were presented at the Australia & New Zealand (ANZ) Cornea Society and Eye Bank Association of Australia and New Zealand Annual meetings in February 2018.
7. Review the benefits and risks of changing the anti-fungal concentrations in the organ culture media.	This was a longer term recommendation for consideration and may not be necessary.
8. Improve the current process of handling of gloves / laminar flow	Local Infection Control Coordinator and Tissue Banks Lab Manager conducted an extensive simulation of the procedure and have refined the procedure.
9. Recommendation to surgeons regarding patient review timelines.	This recommendation is due to the increasing prevalence of candida. This was discussed at the ANZ Corneal meeting. Surgeons felt existing protocols remain appropriate.
10. Donor Assessment	Prior to death, donor 1 had received treatment in intensive care for several weeks, inclusive of significant prophylactic antibiotic use. Following review it was suggested that all Tissue Donor Coordinators and retrievalists should be highly suspicious of at-risk patients and their recent environment. A history of, or evidence of oral thrush represents an additional restriction on donor suitability even if all microbiological testing has proven to be negative up to the time of death and tissue retrieval.

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