Corneal Transplants Outcomes Post-Reporting of Concomitant Potentially Pathogenic Organisms Including Clostridium in Non Ocular Transplant Tissue Results

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Food and Drug Administration, (FDA), regulation 1271 for HCTPs, (Human Cell and Tissue Products), recommends sharing all reports of potential risk of disease transmission or infection with all agencies, i.e. eye and tissue, involved with the donation. This is a recognized part of good tissue banking practices,[1] due to the potential for microorganisms to cause infectious complications in recipients of allograft tissues. Microbes may represent an ongoing infection in the donor prior to death or be a contaminant from external sources. Skin flora or another host source or an organism introduced during graft recovery can be more prevalent on skin and bone allografts than with ocular tissues due in part to post- mortem timing and extended length of necessary operative recovery procedures. Evaluation of bacterial isolates and the determination of risk to tissue recipient is the ongoing responsibility for the tissue or eye bank distributing allografts for transplantation. Of particular concern to tissue banks and to the FDA has been the potential for Clostridium present in or on grafts.[2] This also presents a challenge to the eye bank when a report of Clostridium is received from a tissue source, days after the cornea transplant has already occurred. Other pathogens which must also be evaluated for risk include but are not be limited to Gram negative rods, Staphylococcus aureus, Streptococcus, and fungi/yeast. These organisms are often designated by the tissue banking community as non-compliant organisms, and may result in the discard of certain allograft tissues.

The American Association of Tissue Banks,(AATB), and the FDA have provided standards and regulations regarding allograft- associated bacteria and specifically reference concerns for these organisms;[1,2] ocular tissue complications due to Clostridium isolates have been seen only rarely.[3] Nevertheless, eye banking personnel must appropriately evaluate reports of Clostridium and other potential pathogens obtained from other sources and make appropriate notifications as necessary. This retrospective review of tissue donors of which 1335 were also cornea donors examines corneal transplants with donors of tissue, either musculoskeletal or skin, which had isolates of Clostridium or other pathogens and corneal transplants which occurred prior to report of microorganisms on the tissue allografts. Records from 2011 through June 2017 were examined for ocular post-transplant outcomes. Results suggests a differing infectious risk from external bacteria between ocular tissue and other frequently transplanted allograft tissues, supports the concept of tissue-specific regulation and emphases the need for policies and procedures for reports of potential pathogens in donor associated non ocular grafts.

METHODS

Multiple donor tissues intended for transplantation where standard recovery and or processing cultures had isolated any Clostridium or other potential pathogen, (referred to as non-compliant organism by the tissue banking industry, organisms AATB standards identify as “pathogenic, highly virulent) were reviewed for the comparison with the transplant and outcome as reported in the recipient follow up of cornea transplantation from these donors. This represents 1595 tissue donors and 1335 ocular donors in this review interval 2011 through June 2017 as seen in Table 1.

Skin, bone and connective tissue had representative samples cultured at the time of procurement in Trypticase soy and Thioglycolate broths. Broth tubes were sent to a commercial testing laboratory where they were incubated for 14 days or until growth was observed. Positive tube cultures were sub cultured to blood agar, chocolate agar or

Table 1 *Total Tissue and Ocular Donors from January 2011-July 2017*

	Full Tissue Donors*	Ocular Donors**	Ocular Donors with Tissue Donors Positive for Non-Compliant Bacteria***
2011	197	154	33
2012	226	172	25
2013	182	161	30
2014	258	215	23
2015	296	264	56
2016	299	261	67
2017	137	108	40
TOTALS	**1,595**	**1,335**	**274**

** Full tissue donors includes variations of the following tissues: eye, musculoskeletal, cardiovascular, and skin. Total number of tissue donors excludes all "ocular only" donors*

***Reflects the total number of ocular donors within the number of full tissue donors*

****Reflects the total number of ocular donors with tissue positive for a non-compliant bacterium that were used for transplant. To figure the total number of corneas transplanted, multiple the donor total times 2.*

MacConkeys plates and subsequently identified as to genus and species as appropriate. Grafts with positive organisms which were considered to be pathogenic or non-compliant were not released for distribution, in accordance with good tissue banking practices, AATB Standards, and FDA regulations. Ocular cultures at procurement were not performed and are not required by FDA or the Medical Standards of the Eye Bank Association of America. Poor correlation between procurement cultures and endopthalmitis has been reported accounting for the lack of pre implant culturing.[4] Rim cultures at the time of transplant, however, may be performed by the surgeon.

RESULTS

Clostridium isolates varied in species as can be seen in Table 2 with a mix between the more commonly associated pathogenic varieties to the less frequently seen and often soil or environmental varieties. Eighty-seven of the skin or bone isolates from this group were Clostridium with the highest percentage being Clostridium perfringes as seen in Table 3. Other non-Clostridium isolates as seen in Table 4 included Fungus and Yeast and Staphylococcus aureus as

Table 2 *Number of Ocular Donors with Clostridium Present on Tissue from January 2011-July 2017**

BACTERIA	2011	2012	2013	2014	2015	2016	2017-July	TOTALS
Clostridium perfringens	3	6	8	2	6	7	8	**40**
Clostridium sordelli	1	1	1	1	5	0	2	**11**
Clostridium difficile Colitis	0	2	2	1	0	2	0	**7**
Clostridium sporogenes	0	0	0	0	1	5	1	**7**
Clostridium innocuum	1	0	0	1	2	1	1	**6**
Clostridium subterminale	1	1	0	0	1	0	2	**5**
Clostridium baratii	0	0	1	0	1	1	0	**3**
Clostridium (Unknown)	1	1	0	0	0	1	0	**3**
Clostridium bifermentans	0	0	0	1	1	0	0	**2**
Clostridium septicum	1	1	0	0	0	0	0	**2**
Clostridium tertium	0	0	1	0	0	0	0	**1**
TOTALS	**8**	**12**	**13**	**6**	**17**	**17**	**14**	**87**

** totals represent the number of donors, not the number of isolates per donor, nor the number of corneas transplanted. To get a cornea total you would multiple 2 corneas for every donor.*

Table 3 *Total Tissue and Ocular Donors from January 2011-July 2017**

BACTERIA	
Clostridium perfringens	**14.5%**
Clostridium sordelli	**4%**
Clostridium difficile	**2.5%**
Clostridium sporogenes	**2.5%**
Clostridium innocuum	**2%**
Clostridium subterminale	**1.8%**
Clostridium (not identified)	**1%**
Clostridium baratii	**1%**
Clostridium bifermentans	**<1%**
Clostridium septicum	**<1%**
Clostridium tertium	**<1%**

** Percentage of individual isolates of Clostridium by species as identified from tissue donors.*

Table 4 *Number of Ocular Donors with Non-Compliant Bacteria Present on Tissue Allografts from January 2011-July**

BACTERIA	2011	2012	2013	2014	2015	2016	2017-July	TOTALS
Fungus/Yeast	15	1	5	7	14	16	6	**64**
Staphylococcus aureus	1	6	4	4	6	14	4	**39**
Enterococcus Group D	1	3	1	2	7	6	4	**24**
Escherichia Coli	2	2	1	0	1	4	6	**16**
Pseudomonas	2	0	0	2	3	1	0	**8**
Enterobacter cloacae	0	1	1	0	0	5	0	**7**
Peptostreptococcus	2	0	0	1	2	1	1	**7**
Klebsielle	0	0	0	0	3	2	1	**6**
Sphingomonas	2	0	1	1	1	0	1	**6**
Pantoea agglomerans	0	0	0	0	1	0	2	**3**
Ralstonia picketti	0	0	2	0	0	0	0	**2**
Stenotrophomonas maltophillia	0	0	1	0	0	1	0	**2**
Anaerococcus prevotii	0	0	0	0	0	0	1	**1**
Salmonella	0	0	0	0	1	0	0	**1**
Serratia marcescens	0	0	1	0	0	0	0	**1**
TOTALS	**25**	**13**	**17**	**17**	**39**	**50**	**26**	**187**

**Chart totals represent the number of donors, not the number of corneas total. To get a cornea total you would multiple 2 corneas for every donor.*

Table 5 *Percentage of Non-Compliant Bacteria (Excluding Clostridium) Found in Donors From January 2011-July 2017**

BACTERIA	
Fungus/Yeast	**23%**
Staphylococcus Aureus	**14%**
Enterococcus Group D	**9%**
Escherichia Coli	**6%**
Pseudomonas	**3%**
Enterobacter cloacae	**2.5%**
Peptostreptococcus	**2.5%**
Klebsiella	**2%**
Sphingomonas	**2%**
Pantoea agglomerans	**<1%**
Ralstonia picketti	**<1%**
Stenotrophomonas maltophillia	**<1%**
Anaerococcus prevotii	**<1%**
Salmonella	**<1%**
Serratia marcescens	**<1%**

**percentages based on the total number of ocular donors with other non-compliant bacteria present, not including clostridium*

the predominate organisms. Cultures of tissue allografts may have isolates of more than one non-compliant organism either on the same graft or other graft from the same donor. The organism distribution over years of review is also illustrated in Table 4 and the percent of occurrence is reported in Table 5. No cases of post-operative Clostridium or other microbial infections were reported in the ocular transplant patients. In addition no cases of **endophthalmitis** from any organism were reported in these patients. No primary graft failures from any cause were reported and no re-grafting was required.

DISCUSSION

Endophthalmitis from any source is always a sight threatening complication and may result in the need for long term therapy and even cause blindness in the affected eye.[4,5,6] However, discard of transplantable tissue for the report of microorganisms in other tissues not affecting the ocular allografts is also a cause for concern in meeting the specific surgical needs and elective surgery, i.e. DSEAK, DMEK, demands which require more extensive processing.

Based on the results of this retrospective analysis of 1335 corneal transplants with 274 associated donor positive tissue allograft cultures, it appears recovery of Clostridium or the other isolated potential pathogens from tissue sites not associated with clinical pre-mortem conditions may not pose a risk for post-operative ocular infection. Potential for external contamination of the ocular area, time of death and ambient condition should, however, always be considered in evaluation of donor and tissue suitability as these factors and may influence the presence and genus of microorganisms. Delayed, post-surgical, microbiological results obtained from other transplanting agencies for other allografts though required for good tissue banking practices and FDA regulations appear not to pose an additional risk an increased concern for the implanting physician or a compromised patient outcome in ocular tissue transplantation. Policies and procedures of the individual Eye Bank should address the review of donor history and medical records, and quality policies which will address the handling of these microbiological reports and the medical director's involvement in developing and practice of these policies.

REFERENCES

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