OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee
Meeting Minutes
March 15, 2017
Chicago, IL

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Introduction

The Ad Hoc Disease Transmission Advisory Committee (DTAC) met in Chicago, IL on March 15, 2017 to discuss the following agenda items:

1. Policy Oversight Committee Updates
2. OPTN/UNOS Board of Directors Membership
3. Increased Risk Donors
4. Patient Safety Contact: Preview Programming
5. Cryptococcus Review
6. Abstracts and Publications
7. Member Recognition: Presentation of certificates to outgoing members
8. Histoplasmosis Case Review
9. Classification Rules
10. DTAC Data Requests
11. Current and New Projects
12. Case Review

The following is a summary of the Committee's discussions.

1. Policy Oversight Committee Updates

The purpose and process of the Policy Oversight Committee (POC) was presented.

The current project dashboard showing alignment with the OPTN Strategic Plan goals was reviewed. It was noted that there is space for new projects in OPTN Strategic Goals 3, 4, and 5. The project portfolio is now at 40% for increasing transplant although it had been below in the past. In addition, the safety goal (#4) had also been over allocated, but also has room. This is an area where many DTAC projects have fit. The DTAC project for "Education To Reduce Unnecessary Discard of Kidneys with Small RCC Found Pre-Transplant" was approved by the POC and Executive Committee in February 2017. Other newly approved projects were shown.

After seeing the Minority Affairs Committee project on subtyping, one member shared difficulties for OPOs with subtyping. The member commented that OPOs have issues with interpreting results due to widely varying laboratory nomenclature and questioned the benefit versus risk. Recent OPTN/UNOS educational resources available for subtyping were highlighted. The DTAC Vice Chair indicated that this project could be assessing problems and the project would eventually be going out for public comment. She also will share the members concern with the POC. In addition, the liaison will assist the member in sharing concerns with the Operations and Safety Committee.

2. OPTN/UNOS Board of Directors Membership

The Committee received a presentation about the process for OPTN/UNOS Board of Directors (BOD) recruitment and election. More efforts are being made to assess the needs and effectiveness of this group. Recruitment and call for nominees are starting earlier. In addition,

there is now a preference to have nominees that have previously served on an OPTN/UNOS Committee, as they will be more informed of process and issues.

Some of the overall BOD membership guidelines were shared. There are 42 members of the Board of Directors and the composition is largely influenced by the federal statutes and regulations. The Final Rule and the OPTN Bylaws establish that approximately 50% of the Board must be surgeons or physicians. Among this category, there are certain specialties that are mentioned as well, such as the need for at least one pediatric specialist. The Board attempts to have diversity in the organ specific expertise in this category.

Under the Final Rule, at least 25 percent of our Board must be transplant candidates, recipients, organ donors, or their family members, and certain groups must be represented. These groups include OPOs, transplant coordinators, and histocompatibility professionals. Each of the 11 OPTN regions elects a councilor to serve on the Board. Members are elected to one, two, or three-year terms. The President and Vice-President serve a one-year term. All other members serve a two-year term, except for at-large patient and donor reps who serve a three-year term.

Recently adopted job descriptions for the Board Vice President/President-Elect as well as at-large members were shared. The Vice President/President-Elect must have had prior service on the BOD and either the Membership and Professional Standards Committee (MPSC) or POC. Expectations, such attending meetings including one regional meeting per cycle, are being shared for all who might be considering service. An annual needs assessment is completed in July to help develop a fall slate that can fulfill identified gaps. Some of the needs identified for this year include those with corporate, non-profit governance, finance, and strategic planning experience. The OPTN will develop a new three-year strategic plan in 2018. Goals are also to improve minority and gender representation as well as improve representation from different professional perspectives (e.g. transplant administrators).

Open positions coming up for 2018-2019 will include officers as well as donor and patient affairs representatives with a need for more recipients; at-large MDs practicing medicine, general at-large, and transplant administrators. The call for nominations through Committees starts this month and will expand to the greater community in April. Nominees will be assessed through August and a slate developed that is approved later in the year. The election is held in February/March 2018 with a start date of July 1, 2018.

The Chair encouraged DTAC members to consider this opportunity especially those who will be leaving Committee service this July. Recommendations can be made through UNOS staff (liaisons or regional administrators) or Regional Councilors.

3. Increased Risk Donors

Research presented recent data on the growing issue of drug abuse, specifically the opiate epidemic, and its impact on organ transplantation. A March 2016 Centers for Disease Control and Prevention (CDC) *Morbidity and Mortality Weekly Report* (MMWR) indicated that drug overdoses had risen 137% and opioid overdoses were up 200%. The rise in overdoses points to a start with legitimate prescription pain medications following surgery or injury. Patients often build up tolerance and become addicted. Once the physician stops prescribing, then these patients may turn to the black market for medication or turn to cheaper alternatives such as heroin.

The current state is being described as epidemic. Drug overdose deaths have tripled in the past 15 years. In 2015, 63% of drug overdoses were opioid related. The U.S. Drug Enforcement Agency (DEA) conducts an annual assessment of local drug threats. In 2015, heroin was identified for the first time as the biggest threat. In 2016, it was prescription opiate drugs. Over

the past 10 years, the drug landscape in the United States has shifted, with the tripartite opioid threat (controlled prescription drugs, fentanyl, and heroin) having risen to epidemic levels.

Recently published research by Goldberg (et. al) has shown that the greatest relative increases in the mechanism of death among organ donors were due to drug overdoses. A 350% increase has occurred in the past ten years (2003-2014) going from 138 to 625 donors.

An OPTN/UNOS analysis on deceased donors recovered in the U.S. during 2010-2016 (based on OPTN data as of January 20, 2017) was presented. The data included those donors whose mechanism of death was drug intoxication although the type or dosage of drug is not collected. The data also included donors with a history of intravenous drug use (IVDU). The limitation with this field is that details on the type or dosage of drug, the duration of history, nor how recently the history of drug use occurred are not collected.

DTAC members also noted that drug users who die from anoxic brain injury may have drug histories that are missed due to multiple hospital stays, inadequate sharing of information, and other factors. An OPO representative shared that following an extensive chart review, it was found that closer to 30% of the New York donors reviewed had active drug abuse. The concerns for potential underreporting were noted by many.

The percentage of U.S. donors with drug intoxication reported as mechanism of death rose from 4.3% (2010) to 12.6% (2016). The percentage of U.S. donors with both drug intoxication reported as mechanism of death and a reported history of IVDU rose to 7.2% of all donors in 2016. The hepatitis C (HCV) status of these donors has risen from 10% positive (2010) up to 25% (2016). DTAC members noted that since NAT was not collected until 2015 that these later data might include NAT negative but antibody positive donors who might night be reflective of cleared (not active) HCV infection.

The percentage of U.S. Public Health Service (PHS) Increased Risk donors has steadily increased to 22.2% of all donors in 2015. Not all IVDU or drug intoxication will show up under PHS Increased Risk status. Seventy percent of those with drug intoxication reported as mechanism of death are also classified as increased risk, yet 30% are not because the drugs were not injectable. Some with a history of IVDU will not classify as increased risk because the history is too far back to fit under the definition.

Regional variations were also presented with a heat map showing increases over time on for deceased donors with drug intoxication reported as mechanism of death. The higher rates of both drug intoxication as mechanism of death and history of IVDU are concentrated in the northeast quadrant of the U.S. Over 20 percent of deceased donors recovered in Regions 1, 2, and 9 had drug intoxication reported as mechanism of death in 2016.

The Committee discussed possibly recommending that all transplant recipients get a post-transplant HCV test at two months to help close the gap of those not classified as increased risk. One member suggested a range of two-six months. It was noted that the Committee would not push for policy but might try to provide some type of education for transplant hospitals to consider this. It might make more sense in certain regions or other factors. It could be made part of the current public comment document. It was decided to get some feedback on current practices. If this consideration were shared, it would need to be vetted by all pertinent stakeholders (e.g. Joint Society Working Group) and may still face opposition. The DTAC has some concerns regarding donors who might not fall into increased risk but have some risk due to drug history.

The DTAC does not think post-transplant HCV screening for all or selected groups (other than the current increased risk requirements) should be pursued as a policy option but put forth as a

consideration and to highlight there is a gap that merits testing consideration. Recipients would only need to be tested once, not serially.

The American Society of Transplantation (AST) recently held a consensus conference on HCV. It was mentioned to think about this avenue. It was noted though that the topic of post-transplant screening was not discussed as part of that conference. The issue will be shared with that group by one of the DTAC members who participated in the conference.

Other members noted where anoxia is cause of death and while toxicology screens are performed, that some synthetics do not show up. Toxicology screens are not standardized among labs. The practice of going back to the Medical Examiner for better results was shared. Infectious disease physicians have been asked about the impact or potential risks of using livers from donors with drugs as a mechanism of death. This has been a very hard question to answer. One researcher, Dr. Dory Segev, may have collected but not reported this data.

It was noted that variations in how OPOs report cause of death and mechanism of death could be more standardized to improve data quality.

Members noted how useful and impactful these data are. The CDC weighed in upon request that they do not believe these data are product of an artifact but that they do represent real trends and the transplant data is consistent with the national overall data reported in places such as the MMWR regarding trends in drug use and deaths.

An update was given on the "Guidance on Explaining Risk Related to Use of PHS Increased Risk Donor Organs When Considering Organ Offers" project. The guidance document prepared for special public comment will first be reviewed for readiness and approval by the POC on March 16th and Executive Committee on March 20th. If approved as anticipated, then the special public comment period allowed for guidance documents will begin on March 27 through April 25, 2017. The timeline is shorter than regular public comment, only 30 days. The OPTN/UNOS Board of Directors approved this alternative special process when it also adopted the recommendation that guidance in general go out for public comment.

The document is still on schedule to go to the June 2017 OPTN/UNOS BOD for consideration. Timelines will be very tight. Comments will reviewed by DTAC leadership on a weekly basis. A national webinar is also being held on April 4th for the special public comment as mechanism to reach a wider audience. The full DTAC will have a very short timeframe from April 28th to May 3rd to consider all comment and make post-public comment changes prior to materials being sent to the BOD. The group decided to go ahead and meet on the regularly scheduled date of April 28th at 4 pm EST recognizing that if further comments come in late that day that the group will need to meet again. It was explained that email votes must be unanimous and have 100% participation under Virginia statute so email is an option if those requirements can be met.

More information on the recent HCV Consensus Conference was shared. The Conference included representatives from transplant (kidney, liver, thoracic), OPO, pharmacy, infectious disease, government-Health Resources and Services Administration (HRSA) and insurance. With the advent of new viral drug therapy, the views on HCV infection and use of positive organs have some new considerations. It was decided that with nucleic acid testing (NAT) that the term HCV positive needs to be changed to HCV viremia. Education must be done to help transplant professionals understand the difference between antibody positive and NAT positive. Persons who are antibody positive but NAT negative may be those who have been successfully treated and have cleared the virus. It has only been since August 2015 that HCV NAT was made a mandatory test and data were collected through the OPTN.

Injection drug use will be the main force of viremia donors in next decade and this will likely continue to increase. IVDU donation in the window period (5-7 days for NAT) will be the most

likely unexpected transmissions. Some transplant programs are transplanting HCV positive donors into HCV negative recipients under clinical trials. More data are needed in this case for insurance and government to come on board with this type of use. The recommendation will be that this type of donation continue only under clinical trials or extreme situations for the current time.

It was reiterated that the idea of post-transplant screening of other recipients potentially at risk was an interesting one not yet considered by the consensus group but one that will be brought to their attention. The question of how to handle HCV antibody positive and NAT negative donors with a recent relapse in risk factors was asked. It was noted that recent risk factors do mean risk. For those without current risk factors, NAT negative (antibody positive) organs have been used from living donors with good outcomes.

Plans are to publish the HCV consensus document in a peer-reviewed journal. The current draft will be ready for submission in the next few weeks. It was asked if direct acting anti-virals could be given as a preventive strategy to a donor found with a needle in the arm testing HCV negative. The committee discussed it could be theoretically possible if the virus had reached the hepatocytes since the medication does work in hepatocytes. They also discussed how this would need a study and it would be nearly impossible to conduct. Although the candidate screening was mentioned as an alternative, the member stated that it would help to be able to place the organ from the OPO side. It was also noted that identifying the disease in the recipient at several months post-transplant would be acceptable because generally you do not treat right at seroconversion.

4. Patient Safety Contact: Preview programming

The UNOS Customer Advocacy Director reviewed programming being developed to help OPOs and transplant hospitals better manage and use the patient safety contact list. Currently changes are sent to patient safety staff and then a weekly list in a pdf format is generated and posted in Secure Enterprise. A demonstration of the new prototype was demonstrated. This programming would be done prior and is a first step before programming the post-transplant communication pilot previously discussed with the DTAC.

DTAC members were shown the search screen, how patient safety contacts can be exported to excel along with date and time stamp. This can be done for the entire list or just specific institutions.

The search will take you to an institution where the users can view the primary and back up contact for each organ specific program and each OPO. Phone and email for each contact are required fields. Anyone who can access Secure Enterprise will be able to access this search functionality. A special role would be developed for edit privileges. This role would be granted and managed by the institution's UNet security administrator. A pencil will appear for the editing function. Either the editor can type in contact information or the patient safety contact can be set to the primary on-call person for DonorNet. If the latter is chosen, then the field becomes un-editable.

The back-up contact is not a required field, but if you start editing one field then all three fields will be required. Once the information is saved then the information is updated. The next search conducted will show the real time information with modified date time stamp.

One member suggested not requiring both email and phone because greater flexibility is needed. It was noted that policy does not require phone numbers or fax and operationally these are fraught with problems, while email groups have found to be successful by this member. It was mentioned that for their OPO, the organ specific email groups has not hurt their workload. Email and then a reply also provides written documentation of receipt. Another suggestion was

to allow for organ specific contacts. It was confirmed that this functionality is in the current requirements and will be available. The other feedback on required fields will be shared for consideration.

The DTAC noted that this programming would be a major improvement over the current state. The failure modes and effects analysis conducted by DTAC had identified that the current system is difficult. The DTAC also inquired about the post-transplant communication pilot discussed at a previous meeting. It was shared that this project is still moving forward as a pilot but that the changes to the patient safety contact list functionality would need to be made first. Those changes would be made available to all members. The plan is to ask DTAC for feedback on final post-transplant communication requirements (pilot project). The aim is to get programming slotted by mid-April 2017.

5. Cryptococcus Review

DTAC reviewed recent Cryptococcus cases to identify potential learning opportunities. In 2015, there were four cases with no bad outcomes. In 2016, however, there were eight cases reported. Out of 28 organ recipients, ten were found to be proven or probable (P/P) donor derived disease transmission. Two recipients died. There were seven intervention without disease transmission cases including lung recipients, which are harder to adjudicate.

The DTAC brainstormed to see if there were any patterns or emerging trends. They also noted that a member had also inquired about any patterns due to a perceived increase in their own area. The DTAC discussed the circumstances of the individual cases. It was noted that in Africa the practice of screening serum for Cryptococcus antigen (CrAg) among HIV positive organ recipients and treating positives with fluconazole has resulted in decreased deaths. It was further noted that false positives from Cryptococcus are rare. While it may not be reasonable to screen all donors, screening certain groups such as younger patients with slow neurological decline might have some value. It was noted that several of the recipients studied were relatively young (55 years old or younger) and several had strokes and/or slow neurological decline. The question of the impact of steroids given to donors and their impact was discussed. Potential communication problems were considered.

The difficulties in drawing conclusions were discussed. These types of cases are somewhat similar to syndromic-like encephalitis. For half of these transmissions, there may be no way to know (e.g. an accident victim happens to also have West Nile Virus but never had symptoms). These cases might be a coincidental cluster.

If the donor dies and they have limited pulmonary disease, it is hard to know how many cases are transient that are self-contained and never disseminate.

The other possibility though involves, was something missed in communication, or did some treatment not work?

It was asked if these cases were regionally concentrated. The donor regions involved were spread out between seven, five, and four. The recipients were at various regions. This does not appear to be a regional cluster.

One donor was known to be CrAg positive and the testing was done three months post-transplant.

The DTAC is also interested in knowing the efficacy of azole treatment/prophylaxis. The group found it surprising that there were only five lung recipients involved. They surmised that it might be more typical to give azole prophylaxis to lung recipients that perhaps prevents cases. Members would like to obtain more information on when the affected individuals started azole therapy and was it helpful.

The DTAC identified that getting more information on these cases such as retrospective (CrAg) when this test was not done, autopsy results if available, and initiation of treatment and type of treatment would help more definitively answer questions that these cases have raised.

6. Abstracts and Publications

The DTAC submitted three abstracts that were all accepted for the upcoming 2017 American Transplant Congress. These included:

- "Donor Derived Transmission Events in 2015-2016: Analysis of the OPTN Ad Hoc Disease Transmission Advisory Committee (DTAC)". Will be presented on May 2.
- "Deceased Donors with History of IV Drug Use and Donor Derived Hepatitis C Virus". Will be presented on April 30.
- "10 Years of DTAC Experience with Kaposi's Sarcoma". Will be in poster session on May 1.

The data from these abstracts were presented to the group although these data are embargoed until after the conference. The entire DTAC is an author on the 2015-2016 yearly summary.

The CDC representative asked about if these data had been published as a manuscript recently. It was noted that published US data is outdated. It was shared that 2011 was the last journal publication but that a ten-year manuscript is in the works and thought to be more relevant due to the aggregate number of cases. The CDC indicated support for this effort and volunteered to help with a section devoted to public health investigations conducted on DTAC cases. The DTAC agreed that this would add significant value to the manuscript.

7. Member Recognition: Presentation of certificates to outgoing members

DTAC leadership recognized members with terms of service scheduled to end on July 1, 2017.

These members included Helen Irving, Tammie Peterson, Dr. Joanna Schaenman, Dr. Nicole Theodoropoulos, Dr. Michael Nalesnik, Dr. Daniel Kaul, Dr. Aneesh Mehta, Dr. Ajit Limaye, and Dr. Marilyn Levi.

8. Histoplasmosis Case Review

This project was not discussed with the full Committee as the work group is still working actively on this review.

9. Classification Rules

The DTAC chair discussed the need for more consistency and documentation of class adjudication rules. Changes to how the group processes cases falling within the Intervention Without Disease Transmission (IWDT) category were proposed and discussed.

The Committee often struggles with cases where medication given to recipients should make the case an IWDT. It could be that medication was given for a different reason or was part of a standard therapy but would cover the potential transmission. Whether the reports are based on a donor-identified organism versus another sick recipient, complicate the adjudication.

The idea of trying to distinguish whether a microbial transmission occurred was discussed. In some cases, there might be evidence of a donor-derived organism that was transmitted but that disease did not occur or it was prevented with an effective prophylaxis. It was noted that significant knowledge could be gained and shared if this type of tracking on microbial transmission and prophylaxis were put into place. It could help inform the community better of effective prophylactic strategies.

The idea of subcategorizing the IWDT into disease and microbial transmission subcategories was discussed. This would help answer questions such as how many times do programs take the information received and then act on it, however the more important question that could be answered is how often does a specific intervention work. It is important to know when possible if microbial transmission did occur and that we prevented disease due to the treatment provided upon knowing this information. The current use of IWDT is not as helpful as it might be. One member suggested using the terminology of infection (microbial transmission) versus disease.

Members also discussed the concern that the categorizations if further split might become too complex and more arbitrary over time due to member turnover. The issue of lung recipients was discussed, as lungs are the only non-sterile organ transplanted. Often organisms in the donor lungs will show up on a bronchoalveolar lavage (BAL) routinely conducted several days post-transplant. Often these are routine findings and managed without issue. An example was shared regarding adenovirus. It was asked what should be done in cases where day-two post-transplant adenovirus is found on BAL, but does not cause any problems. We might count this as excluded, yet we miss that the microbial transmission occurred. One member suggested a different strategy for lung classifications. The DTAC has struggled with how to classify these and the value of adjudicating some of these cases.

It was noted that for hepatitis it might take years to develop the liver disease but that the documentation of hepatitis transmission is critical. The concern of the multiple nuances that various scenarios discussed would raise reiterated concerns about too much complexity and data dilution. One person commented that if you detect at some time point donor-derived transmission, then that is important to continue capturing whether they become symptomatic or develop sequelae.

Members identified that the outcome question is a different question. If a system was devised that eliminated all routine bacteria found in lungs from the DTAC classification it would still get harder with lungs for other pathogens such as fungi, viral, and even some bacteria such as tuberculosis. It was decided that this could also turn out to be more arbitrary. Donor derived-prevalence and incidence would then be much harder.

The CDC was asked how they would approach findings in lung on day one or two. From their perspective the agent would not matter, it would be donor-derived. They cited the recent amoeba found in a drowning case. It was mentioned that there is a National HealthCare Safety Network (NHSN) blood hemovigilance module housed at CDC that is used nationally for events such as infection transmitted through transfusion. In this system, there is case definition, severity, and imputability.

The first question about case definition is what to include in the dataset. The imputability is whether the transmission was due to the blood transfusion. Adding a severity designation then accounts for the level of impact to the recipient. Donor-derived transmissions might or might not result in severe outcomes.

Intention is important. Interrupting transmission is important. All the prophylactic medications taken by a recipient are important to know. Not all of this information is getting to the Committee to help inform decisions. Staff also noted that they could get this information as part of 45-day follow-up. There was some discussion about difficulties in getting all needed information and having cases posted within two days. Malignancies could probably be posted on a less strict timeline but potential CDC investigations require timeliness.

The DTAC decided that they like idea of using a severity index to help adjudicate. The discussions from the meeting will be considered before any changes made. More research will be done on adding a severity index as is done for blood transfusion donor-derived infections. It

was noted that the current algorithm was developed to help guide and avoid repetitive debates but that it was not set in stone. It was advised to write down all changes and rules. A long time member did indicate that decision applications drift over time.

The DTAC also discussed the current 45-day follow up and period for adjudicating malignancy cases. Often what happens is the DTAC will exclude-to-date a case but desire additional follow up or leave it open to change since a malignancy might not show at 45 days. Often time to appearance is based on the type of cancer. In reviewing 2008-2013 malignancy data, it was found that usually blood cancers show up early and renal cell carcinoma (RCC) shows up immediately. Melanoma is usually found within the first year post-transplant. In the first two years, the data show that 95% of malignancy cases are captured. A two-year window would make conclusions valid. Beyond two years, very few cases are missed and it is hard to distinguish whether they would be donor transmitted or de novo. For donor malignancies, we do have this information and then we would add the two-year follow up window. For cases that originate with a recipient reporting a malignancy, then we might make the final adjudication several months after follow up is completed on all recipients under the reasoning that the cancers would likely show up around the same time. That is an assumption no research exists to definitively answer this question.

The DTAC plans to keep the 45-day review for malignancies and then determine need for additional follow up at two years. It was noted that the 45-day guideline is not specified in policy but rather policy permits follow up requests needed as part of the investigation. Staff indicated that they could adjust the process. It was also noted that transplant hospitals and patients could benefit emotionally and economically from knowing that screening picks up 95% of donor-derived cases with the first two-years.

It was questioned whether any other adjustments need to be made for other transmissions (e.g. allergies). The time to transmission detection for infections is generally a much shorter window. Ninety percent of bacterial infections will manifest within 30 days. A few types might take longer such as Strongyloides is more around the 90-day mark for symptom onset. One of the longer periods is for aspergillus as there have been some cases not appearing until 9-12 months post-transplant. Tuberculosis is one that will be a longer time to manifest. The DTAC decided to stick with the 45-day follow up and just make adjustments if needed for non-malignancy cases.

10. DTAC Data Requests

The DTAC research analyst reviewed how to put in an OPTN data request and available online data on the OPTN website. It was noted that there could be ad hoc and recurring data requests. Programs can request individual data for their own programs as well as receive aggregate data. There is Standard Transplant Analysis and Research (STAR) file provided upon request that contains nearly all variables available. The STAR file comes with a data dictionary. For other information, the Transplant Pro site was shown where all OPTN forms are available to view what is collected and available. UNOS staff are available to assist. For complex analyses, staff can assist for a fee depending on time and effort involved. DTAC members found this very helpful.

It was discussed that members are in a unique situation being on DTAC. It is important to remember that DTAC members have access to more specific data. Data can be used but anything that has not been publicly presented must go through HRSA approval first. HRSA also must approve any external data requests that would involve identified data.

Review prior data request findings

The group reviewed prior data request findings. The first data request reviewed was a policy post-implementation evaluation that actually wrapped up three projects. In August 2015, IT programming was released to implement:

- Proposal to Modify OPO and Transplant Center Requirements for Screening, Communicating and Reporting All Potential or Confirmed Donor-Related Disease and Malignancy Transmission Events (2010-qualified specimens)
- Proposal to Modify Deceased Donor Testing Requirements (2013)
- Proposal to Align OPTN Policies with the 2013 PHS Guideline for Reducing Transmission of Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) Through Solid Organ Transplantation (2014)

The data analysis looked at the "Hemodiluted Specimen?" field now required for all infectious disease test results entered. The policy evaluation question is: "How many hemodiluted samples used and how many resulted in a patient safety potential donor derived disease transmission report? Findings are that there have been ten donors where a hemodiluted HIV Ab/Ag sample was used (five different OPOs). There were also 237 donors tested for HIV NAT using a hemodiluted specimen (48 different OPOs). Of the total 238 unique donors, two donors were reported as potential donor derived transmission events (PTDDE). These cases were not for HIV and both were found to be excluded. There have not been any PTDDE for HIV since the policy went into effect.

Members commented that these findings were reassuring that the way we do business is fine. The data do not indicate that tests are resulting in known false negatives. An OPO member commented that answering the questions of whether a sample is hemodiluted is a huge amount of work on a very complex calculation that often results in audit findings. It was questioned whether in the age of NAT, is this policy is still relevant? It was asked if this is a theoretical problem or one based on experience? Some lab experts have expressed some skepticism that current testing will perform more poorly on hemodiluted specimens. The policy was developed and passed several years ago. The DTAC plans to form a small work group to discuss these issues further and bring back findings.

The second part of the data request reviewed use of the HIV combo Ag/Ab that can be used in place of the antibody for screening as well as for increased risk donor testing. Overall, there were 412 donors screened with the HIV combo Ab/Ag from 25 OPOs. All OPOs have some donor results using HIV NAT and 56 OPOs used antibody screening. There were 339 donors from four OPOs using the HIV combo Ag/Ab test but not the antibody screening. There was one OPO using only the HIV combo Ab/Ag test versus NAT on 139 donors.

The data indicate that testing is taking place as policy requires and that most OPOs have found ways to perform NAT testing which had been an earlier concern due to finding laboratories that can perform this type of testing. It would appear that most are using laboratories that conduct Triplex testing (NAT that can detect HIV, HBV, or HCV). There have not been any PDDTE for HIV since this policy was implemented.

One member asked how long the HIV combo Ag/Ab might still be manufactured in the U.S. It was not known but surmised this may still be produced to help meet blood banking needs, CDC did recommend switching over to NAT. With the increase in IVDU, it might not be as reassuring but it does give OPOs an option but most have found a way to perform NAT. The HIV combo Ab/Ag test does have a slightly bigger window period than NAT. The DTAC decided that this data does not need to be reviewed any further as part of post-policy implementation evaluation.

The data request also looked at reports and findings for 12 HBV; 12 HCV; and 3 HIV PDDTE where available adjudication data was readily available. Of these reports, there were four P/P cases (2 HBV and 2 HCV). All recipients were reported as alive with functioning grafts as reviewed on follow up forms. The DTAC decided that this data does not need to be reviewed any further as part of this post-policy implementation evaluation. They will continue reviewing other data as needed and related to other concerns (e.g. IVDU).

A HOPE Act update was given. There are 32 Approved Programs (29 DD, 3 LD) among 16 Centers (as of 2/17/2017). In 2016, 11 HIV positive deceased donors were recovered. There are 118 candidates (112 kidney, 6 liver) HIV positive candidates on the waitlist willing to accept a HIV positive organ. In 2016, there were 24 deceased donor (17 kidney, 7 liver) HOPE Act transplants.

DTAC members who also participate in the HOPE Act did discuss that there appear to be a fair number of false positives that are now being used in HOPE Act transplants. These organs might have otherwise not been used. One member commented that at this point due to the small numbers it does not seem that organs are being siphoned away from the regular list. It was also noted that the anticipated flow of offers and volume has not quite materialized yet due to multiple factors including some state laws that have added complexities.

Members also looked at a post-transplant malignancy analysis to see where malignancy reports originate (patient safety PDDTE portal versus TIEDI follow up forms). These data are reviewed to see if DTAC is missing cases or if members are aware of reporting requirements.

Data on reported malignancies from 2008-16 were analyzed. Eighty-one percent were reported to the patient safety PDDTE portal only; roughly, 10% were reported on a TIEDI follow up form only, and roughly, 10% were reported on both. The mean and median time from transplant to malignancy on the TIEDI follow up forms was about 2500 days.

Members are still reporting primarily to the patient safety PDDTE portal. This trend has not changed. It would be too much work to try to coalesce into one type of reporting. DTAC decided that since they are changing and extending follow up time to 2 years for PDDTE reports that they do not need to review this data again.

Developing the item 23 for policy evaluation of the policy implemented last year (plus toxoplasma April 2017) will be postponed to a future meeting discussion due to time.

11. Current and New Projects

<u>Toxoplasma update</u>

Screening for toxoplasmosis on all deceased donors is scheduled to go live on April 6, 2017. Members were given a demo on how the DonorNet will look. This release will implement the last piece of the comprehensive reporting policy changes passed by the OPTN/UNOS BOD in June 2016. The toxoplasma IgG is not required for match and may not come back before transplant. The Committee does not want any unintended discards. There is an educational product in UNOS Connect that explains the need and benefits of toxoplasma screening as well as discusses prophylaxis for all organ recipients (not just thoracic). Toxoplasma IgG results will appear on a printable donor summary. Talking points that summarize the UNOS Connect module are also being finalized as a resource. DTAC infectious disease members were reminded that they might get more questions about what to do and how to handle toxoplasma from transplant personnel considering offers and caring for patients post-transplant.

Infectious Disease Verification

DTAC has been asked to provide two representatives for the Operations and Safety infectious disease verification project. The project is seeking to develop a policy that would require a process to check infectious disease results. It was referred to the Committee following three living donor near-miss/actual HCV disease transmissions due to human process errors. The project went for public comment once but received significant comments opposed to the proposed policy. The Committee is reworking a potential policy project and adding representatives from MPSC and DTAC to help build support. Drs. La Hoz and Theodoropoulos were thanked for volunteering to be part of the group.

Next steps RCC data and project

The DTAC RCC project was approved as mentioned in the POC update. A work group has been formed and will be working to update data first collated several years earlier.

The analysis will focus on how often kidneys with small RCCs are not used. An earlier DTAC effort had looked at literature and data on 61 recipients that had RCC but had these resected prior to transplant. The Israel Penn International Transplant Tumor Registry (IPITTR) had published against using these kidneys but then changed their position to reflect that kidneys 3.5 centimeter RCC tumors or smaller might be OK to use.

In the earlier DTAC effort, four risk categories were analyzed. The case studies were based on size and limited to well-differentiated, small (2.5 cm or less), single tumors, using a Fuhrman grade which has not been revised. In Europe, it has been reported that using up to 4 cm in size might be acceptable. A manuscript was started in 2011 from then DTAC members including Dr. Martha Pavlakis but not published yet. Dr. Pavlakis will help with the current effort along with Dr. Nicole Turgeon. Both are currently on the Kidney Committee.

Previous data showed 21 cases where the kidney with the tumor was discarded but the contralateral kidney was used and no RCC developed. There were 33 cases where both kidneys were discarded (unilateral RCC in all cases). There were no cases of RCC in the recipients of the other organs. In 13 cases, both kidneys were used. There was RCC transmission in two cases (had not been suspected in donor, therefore not resected). There were seven recipients with RCC at 9-17 years after transplant. Seven donors had suspected RCC, yet found benign on final pathology.

DTAC will be updating the original analysis and working up the data for a potential guidance document. The work group will start meeting soon. The timeline would be to have a product ready by the internal deadline of June 19, 2017 in time for fall public comment.

SPS update

The CDC provided an update on the public health investigation into organ preservation solutions believed to be contaminated.

In December 2016, the CDC was notified of foul smell coming from an organ preservation solution (SPS-1) during organ procurement procedure in Iowa. The procedure was halted. Opened bags tested at the clinical laboratory were positive by Gram stain for Gram-positive and Gram-negative bacteria. *Pantoea aggloremans*, *Enterococcus, and Streptococcus mitis/oralis* were identified. The facility notified the US Food and Drug Administration (FDA), the Iowa Department of Health, and CDC. Initial reports indicated that 14 patients at the transplant center had received possibly affected organs and that four had fever or other adverse events possibly related to contaminated preservation solution. Pantoea aggloremans isolates from multiple samples were submitted to CDC for molecular typing and had indistinguishable PFGE patterns.

Public health authorities investigated the possibility of either an infection control breach during transplant/procurement or contamination of preservation solution during manufacturing.

Two days after the event, the CDC issued an Epi-X with input from the FDA, HRSA, and the OPTN regarding the suspected polymicrobial contamination in the two lots. The recommendation was to not use solution from these two lots and to return them to the manufacturer. These lots were voluntarily removed by company, Organ Recovery Solutions (ORS). The OPTN disseminated the Epi-X to the transplant community.

UNOS forwarded 31 reports involving potential adverse outcomes and SPS exposure involving 124 recipients nationally to CDC. Of the 31 reports, 22 of the reports involved 25 recipients with some concern of potential infectious disease in the originating report. There were also nine adverse noninfectious event reports. None of the adverse outcomes has been linked to SPS to date.

In January 2017, the Iowa Department of Health asked CDC to assist with a field investigation to better understand possible contamination routes during distribution and use of SPS. CDC did not identify any infection control breaches at the OPO or transplant facility. Among 15 patients at the reporting facility who had received organs exposed to these two lots of SPS-1, two had adverse events (such as fever or focal infection) but none were definitively attributed to contaminated preservation solution and no organisms were identified on multiple cultures of various types of body fluids. The CDC did not observe an elevated rate of adverse events during the time the affected solution was used.

Later in January, CDC was notified of foul smelling solution in Texas that involved two additional lots. Another Epi-X also disseminated by OPTN. On January 28, 2017, the CDC posted a final Epi-X recommending use of an alternate solution. ORS stopped production of the solution pending additional investigation.

The FDA investigation is currently ongoing, and the FDA released a safety communication on March 9 to heighten awareness about the potential for bacterial contamination of SPS-1, provide recommendations to health care facilities to help mitigate potential patient exposure to infectious bacteria, and call attention to the manufacturer recall of specific SPS-1 lots. Information released on March 7, 2017 by the manufacturer reported bacterial contamination from two of four removed lots (one in Iowa and one in Texas). The company is conducting additional sterility testing and a root cause analysis.

Results are expected at end of this month. Testing involves another solution (KPS) where random testing for sterility is being done at the same plant.

The FDA investigation is currently ongoing.

12. Case Review

The DTAC reviewed 2016 case reports of potential donor derived disease transmission.

Upcoming Meetings

- March 28, 2017 (Monthly case review teleconference)
- April 11, 2017 (Monthly case review teleconference)
- April 25, 2017 (Teleconference)

Attendance

- **Committee Members**
  - Cameron Wolfe
  - Marian Michaels
  - Helen Irving
  - Daniel Kaul
  - Ricardo La Hoz
  - Marilyn Levi
  - Kathleen Lilly
  - Ajit Limaye
  - Aneesh Mehta
  - Michael Nalesnik
  - Tammie Peterson
  - Robert Sawyer
  - Nicole Theodoropoulos
  - R. Patrick Wood
- **HRSA Representatives**
  - Joyce Hager
- **OPTN/UNOS Staff**
  - Tory Boffo
  - Marissa Clark
  - Maureen McBride
  - Susan Tlusty
- **Other Attendees**
  - Sridhar Basavaraju