OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee
Meeting Minutes
October 19, 2017
Conference Call

Cameron Wolfe, MD, Chair
Marian Michaels, MD, MPH, Vice Chair

Introduction

The Ad Hoc Disease Transmission Advisory Committee met in-person in Chicago, Illinois on 10/19/2017 to discuss the following agenda items:

1. Policy 15.3 Informed Consent Proposal
2. Hepatitis C and Organ Donation
3. Review List of Special Pathogens and Classification Rules
4. RCC Guidance
5. Data Requests and Policy Evaluation Reviews
6. Granulomatous Case Review
7. Peanut Allergy Case Review
8. Cryptococcus Case Review
9. Confidential Medical Peer Review
10. Other Business

The following is a summary of the work group's discussions.

1. Policy 15.3 Informed Consent Proposal

Summary of discussion:

The Committee discussed the informed consent proposal under development. The Joint Societies have elected to name representatives to the existing DTAC work group. Chris Sonnenday, MD will be the representative from the ASTS. Marian Michaels will serve as the AST representative.

The OPTN policy development process was reviewed. This project is in the evidence-gathering phase. Comments from the Policy Oversight Committee (POC) when the project was approved in July were reviewed. The project was started following a referral from the Membership and Professional Standards Committee (MPSC) regarding issues in interpreting OPTN Policy 15.3: Informed Consent of Transmissible Disease Risk. The policy states that, "Transplant programs must obtain specific informed consent before transplant of any organ when any of the following occurs: The donor has a known medical condition that may, in the transplant hospital's medical judgment, be transmissible to the recipient, including HIV." The question has arisen whether this includes common infections such as CMV or EBV. DTAC leadership has indicated that this was not the intent of the policy but acknowledges that the language is vague.

The project timeline was reviewed. POC approved the project in July 2017. DTAC will develop the proposal with the goal of sending a public comment proposal back to POC in December for January 2018 public comment. DTAC will consider public comment at their spring in-person meeting and plans to send a proposal to the OPTN/UNOS Board of Directors in June 2018.

The group considered various policy options including:

1. Completely eliminate vague language for additional risk identified prior to transplant and conditions that might be transmittable in the transplant centers medical judgement

2. Limit conditions to positive tests for HCV and HBV
3. If so, then what tests?
4. Use Special Pathogens list as proxy for conditions (this option previously ruled out by work group)

Members identified and discussed many issues that could affect the proposal including:

- Making policy the minimum acceptable standard and enforceable
- Informed consent discussion prior to transplant of organ with documentation in chart versus signed document
- State informed consent laws
- Informed consent required by CMS CoPs
- Other related and relevant OPTN policies (Policy 5.5 Re-Execution of the Match Run and General Bylaw Appendix L.15: Public health and safety)
- UNet product liability
- Concerns for patient safety that although consent might be difficult it should be done
- Concerns that it is not possible to consent for all potential conditions and that specific conditions should not be part of policy
- PHS Guideline Recommendation 14

It is proposed that the general risk section that already exists will be moved up to the front of the policy. The rationale is that this occurs first chronologically but that also the best time to have the bulk of the informed consent discussion is when the patient is considering being waitlisted versus a rushed middle of the night conversation when a specific organ offer becomes available.

The group discussed which illnesses for which consent at the time of organ offer should be obtained. It was noted that HIV has its own separate policies in accordance with the HOPE Act. It was noted that PHS recommendation 14 states that "When organs from HBV- or HCV-infected donors will be used, the transplant center team primarily responsible for the patient's care should have an informed consent discussion with the transplant candidate, or medical decision maker, prior to transplantation regarding the risks related to disease transmission." One question here is: What does HCV and HBV infected actually mean in the age of serology and NAT?

The group discussed whether informed consent might be interpreted as a separate document. Some on the group however believe informed consent to be a documented discussion although others believe that an actual signature must be obtained. Informed consent forms are used to document the conversation and that it is a legal document. A signed form from the legal standpoint is the best case for informed consent because there is no question about what was communicated. When discussed and documented in a medical note there can be a question about how much the patient understood. Electronic health record (EHR) documentation might be the next best thing commented one member. It was noted that informed consent is an area already heavily regulated by states. The Committee was advised to be specific and not to duplicate state efforts. The proposed policy language will eliminate the word "specific" to allow for flexibility.

The issue of how hard it is draw the line of conditions that need consent versus those that do not was raised. In addition, members noted that the "transmittable" part is also difficult to enforce. Members did comment that regardless of policy it does not take away any standard of care responsibility to discuss potential concerns with patients. It was noted that hospital policies or OPTN policies could be used to determine what the standard of care is. In addition,

vagueness creates potential or unintended consequences and guidance is needed. One scenario where UNet can be programmed to match policy but in the past had not been programmed to notify transplant hospitals when results changed was also mentioned.

The ASTS perspective was presented. They strongly believe that guiding principle should be proportional to patient risk. HBV and HCV are reasonable risks because they affect listing decisions and affect access to transplant. Other conditions are rare events and impossible to cover in policy language. The language does need to be appropriately broad to provide appropriate education and stress that there is uncertainty in transplant. More specific policy language would be a huge burden on transplant hospitals and will discourage people from accepting organs that could save their lives.

It was noted that since the revised PHS Increased Risk guidelines came out (2013), that the conditions it addresses have become curable or manageable and that these are not the conditions causing cause death. It was also noted the need to obtain consent prior to use of PHS Increased Risk organs is currently in policy and will stay in the policy.

One HRSA representative advised that DTAC should be aware of the informed consent provision under the CMS Conditions of Participation (CoPs) 42 CFR 482.102. It requires transplant centers to implement written protocols related to informed consent regarding organ risk on several fronts. It was noted that the OPTN policy might be viewed as a redundant provision. It was also mentioned that HCV and HIV are rapidly changing fields and therefore if policy or regulations become outdated it still takes significant time to change them.

It was also noted that although some expressed concern about vague language creating enforcement challenges that there might be a counter argument to have something on the books to say we expect informed consent. Even if not easily enforceable, there might be a problem if a transplant center does not act properly and then the consequence of how that might reflect on the OPTN. It was questioned why it would seem onerous certain things should be disclosed to recipients to inform patients. It was noted that this issue is one to be grappled with rather than be silent.

It was emphasized that patients should be fully informed and that disease is an inherent risk of transplant but that explaining or consenting all individual risk is not likely achievable in a comprehensive way. The example of *C. difficile* was cited. Members were asked to be mindful of unintended consequences of this policy. One person commented that we might have cost lives due to PHS Increased Risk labeling and the discussion that goes along with it, through increased organ discards, and that by extension we should be careful not to create a situation where patients will refuse likely good organs because of undue concern. It was commented that patients might not understand if too much information is given and that we cannot forget goal of more transplants and saving more lives.

The work group will continue to meet. The goal is to have the full Committee vote on a public comment proposal at their December 12th teleconference.

2. Hepatitis C and Organ Donation

Summary of discussion:

DTAC member and hepatologist, David Goldberg, provided an overview of the etiology and epidemiology of hepatitis C. HCV lives in liver and it does not integrate into genetic code. It is curable. Two-thirds of those with HCV are chronically infected and one-third spontaneously clear the infection. Approximately 1 to 1.5% of the U.S. population is infected. HCV does not reactivate. Before 2011, the cure rate was under 50% but has now risen to over 95% now with new treatments on the market. These treatments cost between $25-90,000 per round of

treatment. HCV infection used to be the number one reason for needing a liver transplant, but now it is NASH. Although about 5% of the current kidney waitlist are HCV infected, only 1.8% opt in to receive HCV infected donors.

Differences in test types and results meaning (antibody-Ab versus nucleic acid testing-NAT) were reviewed. It was noted that antibody positive/NAT negative was thought not to pose transmission risk since the negative NAT result would indicate that no active virus was found. In 2015, UNet[sm] allowed data collection to differentiate between Ab and NAT results and willingness to accept organs with varying results. From HCV viremic (active virus/NAT positive) donors, there has been higher utilization of livers yet two-thirds of kidneys are discarded. Lungs and hearts had been nearly universally discarded until the past 6-9 months. HCV Ab positive/NAT negative donors have typically been utilized similar to NAT positive cases. There are three clinical trials using HCV viremic donors for HCV negative patients with treatment for the resulting HCV transmission. Use of HCV Ab positive/NAT negative donors has been slowly increasing. Transmission risk considerations include potential window period infection (new), false negative NAT results, low-level virus, and reservoirs of HCV (intra-or extra hepatic) that reactivate. Although the last scenario is not thought to be likely there has been some findings of potential negative reverse transcription of HCV not detectable in blood from HCV study cases. Other findings might also suggest passive transmission of HCV Ab that wanes later in recipients.

Two CDC guests, Tonya Hayden and Saleem Kamili, provided information about the additional testing and capabilities that CDC offers and uses with some DTAC cases. The CDC tests serum samples using a FDA approved test. They also however test splenocytes and lymphocytes, when samples are available, using NAT extraction and testing validated and developed within CDC labs. They perform PCR for HVR1 and NS5B and then next generation sequencing and phylogenetic analysis. Often the viral load found in splenocytes and lymphocytes is too low to allow for genotyping. It is also not possible to differentiate antibodies based on genotypes. Previous CDC experiments have found that HCV transmission is not dose dependent and a small inoculum can cause full-blown HCV.

It is not always possible to estimate how long an infection has been present although the CDC can estimate whether an infection is in the acute phase. It is also possible to look at sequencing and whether there has been intermingling with various sources of HCV or if it is a same source.

The group then moved to confidential medical peer review.

The CDC discussed how much they should continue to be involved in HCV and HBV reports. They have published increased risk data that helps quantify risks from specific behaviors. It is uncertain if investigating HCV reports from increased risk donors who are active intravenous drug users will add to the existing body of knowledge.

DTAC members shared the value that CDC has brought to the case findings through additional testing and subject matter expertise. DTAC members brought up that with the recent increases in the opioid epidemic and increased risk donors that the risk figures currently in use might need to be re-evaluated or revised, as they might not be capturing the current situation. The CDC and DTAC members together decided that they would evaluate HCV and HBV reports on a case-by-case basis.

DTAC members noted that the HCV data is critically important to the liver community and that it is the subject of plenary talks at major conferences. Another member brought up the recipient impact and that although the condition is treatable that there are still long-term implications such as health, life, and disability insurance. In addition, the importance of the Final Rule and public

health implications were discussed as these infections impact the home environment and possible transmission to other family members.

The DTAC will plan to form a HCV work group to discuss community needs regarding emerging issues such as transmission from HCV Ab positive, NAT negative donors. A letter to the editor of the American Journal of Transplantation is being published to clarify that transmissions from these types of donors are considered unexpected events and that these should be reported to the OPTN Improving Safety disease transmission portal.

Issues that the work group will explore include the numbers and characteristics of recent HCV transmissions, the impact of when donor samples are drawn and tested, the need for additional guidance on post-transplant recipient testing, differences in transmission among organs, and the need to reevaluate increased risk estimates among IVDU donors.

3. Review List of Special Pathogens and Classification Rules

Summary of discussion:

No additions or deletions were proposed to the list of special pathogens. The notes will be amended to clarify that suspected transmissions from donors who are HCV Ab positive, NAT negative are considered unexpected events, and that these should be reported to the OPTN Improving Patient Safety disease transmission portal.

DTAC leadership is proposing adding a severity to index to help illustrate the impact of disease transmission on organ recipients. The current classification scheme does not adequately reflect outcomes (e.g. death, graft loss). The CDC measures both imputability and severity for blood product transmissions. Using the DTAC algorithm, cases that are proven, probable, or possible might also have an additional severity index of death, severe, non-severe, non-evaluable, or potential for late morbidity. Intervention without disease transmission (IWDT) might have an additional severity index of non-severe, not sure if Rx needed; non-severe, but treatment needed; or severe. Unlikely or excluded would not require an adjudication.

The potential advantages of adding a severity index include the ability to rank critical transmission events, with some clinical judgment. It could help demonstrate, for example, that a pseudomonas bacteremia with a recipient death is more detrimental than a CoNS bacteremia with a non-severe outcome. Severe would be measured using measures such as a prolonged hospital admission or readmission. A non-severe finding would be one where a simple treatment could be administered to prevent or treat the agent of concern. It would help with stratifying IWDT cases. For example, a transplant nephrectomy in response to donor malignancy would be considered severe.

The disadvantages might be the additional resources (e.g. time) to complete an extra severity adjudication. Another question would be whether and when to restart assessment to add severity to cases in the existing database. It might make sense to do this when the policy change to reporting was implemented (September 1, 2016). The goal is to provide more granularity and more meaningfully communicate outcomes.

Prior to implementing this change, it would be necessary to discuss with UNOS member Quality as they were considering adopting a severity index for patient safety cases to discuss any interactions. Modifying the current DTAC database would also be another issue to be researched.

For the current classification, members discussed the issues with a pathogen versus disease transmission. This separation is difficult to achieve. Members also requested a written definition for what is not a case to help apply the rule consistently.

4. RCC Guidance

Summary of discussion:

A work group comprised of DTAC members as well as two Kidney Transplantation Committee members is continuing to analyze data on all RCC cases from 2008-2016. The findings will be developed into a guidance that can help inform the transplant community about potentially using organs from donors who have small RCCs that can be excised. The goal is to have the full Committee vote on a public comment guidance document at their December 12 teleconference.

A former DTAC and current Kidney member, Martha Pavlakis, joined the meeting to provide an update. This project was originally started in 2011 and restarted this year following POC approval. Work group members did a case abstraction to confirm size, histology, recipients, and outcomes. Outcomes are being further analyzed by group such as both kidneys discarded yet a non-renal organ was transplanted or the kidney with RCC was discarded but the contralateral kidney was transplanted. Data are being cross-referenced to other OPTN post-transplant malignancy and follow up reports.

The work group will continue to analyze findings and develop a draft guidance document. The goal is to have the full Committee vote on a public comment guidance proposal at their December 12th teleconference.

5. Data Requests and Policy Evaluation Reviews

Summary of discussion:

Two official policy evaluations were reviewed to look at intended and unintended policy impacts. Policy analysis from the DTAC proposal to re-execute the match run (REMR) showed that post-implementation matches run without HCV, HBV, or HIV results were reduced. During 2012-2013, 21% of match runs had pending HBV or HCV test results at the time of acceptance. The goals of the REMR policy proposal were to reduce potential for unintended disease transmission (PDDTE) and avoid loss of donors, increases in discarded organs due to policy. The policy was evaluated by analyzing:

1. Counts of match runs with HBV+/HCV+ donors (or CMV+ intestinal donors) that have a documented acceptance and in which the donor was not listed as positive (or negative)
2. Discard rates (among organs recovered for transplant) among all donors that had an incomplete-result match run with documented acceptance (Don't want to add time to the process)

Data showed that there were more match runs after policy implementation (n=3,378) than before (n=2,611), but fewer cases where there were incomplete results (n= 214 vs. n=139). There was a significant reduction in the proportion of organs accepted without a result (8.2% vs. 4.1%). Most of the offers being accepted without complete testing were liver offers. This might be because positive hepatitis C or B is a common reason for needing a liver. Discard rates did not appear to be affected the policy change. This was an initial concern with requiring a match run to be executed when results changed to positive yet the before rate (10.3%) and after rate (10.7 %.) did not significantly change.

Many policies could be affecting discard rates but this analysis is only for positive donors and it did not have significant impact on discard rates. Members commented that it appears the policy is doing what it was intended to do. It is not feasible however to evaluate donors where no organs were recovered from OPTN collected data. Members commented that they rarely encounter donor that does not have serologies as OPOs have become very efficient in testing donors. One other observation was that recovering spleen samples has become less prevalent

and that the community might benefit from reconsidering this with the growing numbers of increased risk donors.

Data evaluation from the improving post-transplant reporting policy proposal shows that unnecessary reporting has been reduced in one region. Between 2011 and 2014, the number of reports made to UNOS/OPTN has doubled. The goals of the policy proposal were to reduce unnecessary reporting, clarify reporting protocols, reducing varying interpretations, and shift the reporting focus from donors to recipients. A large number of reports came in at the end of 2016, making changes in the total number of cases difficult to discern. Moreover, many of these reports were not selected for review. At the end of 2016, fewer than half of the incoming reports were selected. As a result, the proportion of cases reviewed by DTAC actually fell by a significant amount, from 73.6% of the 405 reports to 65.2% of the 445 reports in the 13 months before/after policy implementation. The biggest reporter in the pre- period submitted 76 reports, of which 26 (34.2%) were selected for review. After implementation, that OPO submitted 14 reports, of which 13 (92.9%) were selected for review. On the other hand, another OPO from the pre-period, with 6/16 reviewed reports (37.5%), became the top reporter after policy implementation, with 7/66 reviewed reports (10.6%). In summary, total reporting volume has not changed substantially. Fewer cases have been adjudicated with “Excluded”. Many centers are reporting differently than they were before the policy was implemented (e.g., Region 3). A larger share of reports are for recipient results versus donor results. The variances once observed among regions have flattened out.

The Committee indicated that they do want to continue monitoring these two policies again at the two-year mark. The Committee discussed other data requests. These included looking at the cohort of donors (HCV Ab positive/NAT negative) to analyze recipients that had a negative serostatus at transplant but on later follow up appeared to have seroconverted.

Upcoming changes for TRR forms (addition of HCV and HBV NAT) were reviewed as well.

The Committee discussed adding a policy evaluation component to measure the impact of toxoplasma screening. There is some concern that because of anecdotal reports if calls to infectious disease specialists that some organs might have been turned down due to positive results and lack of knowledge about prophylaxis. Although there was an educational effort at the time the screening went into effect, there might need to be other efforts.

Formal data requests will be developed and submitted.

6. Granulomatous Case Review

Summary of discussion:

The histoplasmosis (granulomatous) case review is continuing to work on data abstraction and summary. They are looking to answer questions such as what is the impact of finding a granuloma in a donor; what does it mean for the recipient and does the type of organ recipient affect outcomes (e.g. lung vs kidney recipient). Often infectious disease specialists will receive these questions during donor evaluation and the DTAC data could help guide more informed answers. Once these data are compiled and analyzed, they will be developed into an abstract for ATC or ID week.

Members were reminded that abstracts do need internal staff review. If an abstract is accepted for a poster or plenary session, then HRSA must review and approve all materials to be presented. In addition, all data findings are presented in a de-identified aggregated manner to maintain confidentiality.

7. Peanut Allergy Case Review

Summary of discussion:

A work group is currently analyzing all reported cases of peanut allergy. Plans are to submit an abstract to ATC and consider how this finding is reported in Donor Net. It was noted that during data abstraction that notes about allergy might not be as evident as they might need to be. In addition, recipient centers might not know to search for this information. Transplant hospitals might not be thinking in terms of transmittable allergies as it would seem that shellfish, contrast dye, or penicillin allergies might have been transmitted yet no such reports have been made. It was noted that this discussion might be appropriate not only for an abstract but also perhaps as a regional update or through the Collaborative Transplant Study (CTS).

8. Cryptococcus Case Review

Summary of discussion:

Cases of Cryptococcus from 2009 to present are being reviewed. Notable issues seen include communication failures as well as recognition of potential problems. This review is a possible ATC abstract and work group members will work to have data abstraction finished in mid-November to allow for analysis and write up time.

9. Confidential Medical Peer Review

Summary of discussion:

Members were reminded that they are reviewing materials protected under confidential medical peer review. Members cannot discuss case materials in any way outside of DTAC. Members were asked not to download materials containing confidential medical peer review information or if downloading was necessary that all materials be destroyed in a secure manner as soon as the review is completed. This has become increasingly important as cyber threats continue to grow.

10. Other Business

Summary of discussion:

Autopsy Timelines: Research will work on a data request and analysis to identify the frequency of autopsy in deceased donors.

Extra Vessels Label: DTAC reviewed potential options being proposed by the Operations and Safety Committee to revise the extra vessels label. DTAC recommends that the label be limited to HIV, HBV, and HCV results since there will be a bar code scan to access other results and that too many results might actually add risk to skipping over relevant results. In addition, the Committee commented that other results such as those for CMV would not prohibit use of vessels in an emergent situation but it would guide post-transplant treatment or prophylaxis. One member suggested that someone at the transplant hospital be assigned to update the vessels results. Another member commented on the need to keep the requirements simple as most vessels are destroyed and transplanted in the recipient that received the donor organ with the same information.

UNet^{sm} updates: UNet updates were given for several projects. The pilot to communicate results received post-transplant is still progressing with aim to start in early 2018. Charts showing infectious disease tests captured in various donor and recipient forms (e.g. DDR, TRR, and LDR) were reviewed. A project to update these forms is in flight and will add toxoplasma IgG results to the DDR. HCV and HBV NAT results will be added to the TRR. Five new infectious disease results will be added to the DonorNet infectious disease page in December. The five tests are currently on the DDR and include WNV serology and NAT, Chagas serology and NAT, and HTLV NAT. This is being done as part of a customer advocacy project resulting from a member request at the annual NATCO meeting.

Upcoming Meeting

- TBA

Attendance

- **DTAC Members**
  - Cameron Wolfe (Chair)
  - Marian Michaels (Vice Chair)
  - Remzi Bag, MD
  - Gerald Berry
  - Jamie Bucio
  - Diana Florescu
  - David Goldberg
  - Chak-Sum Ho
  - Ricardo La Hoz
  - Kathleen Lilly
  - Maricar Malinis
  - Aneesh Mehta
  - Michael Nalesnik
  - Robert Sawyer
  - Lynne Strasfeld
  - Nicole Theodoropoulos
  - Patrick Wood
  - Martha Pavlakis
  - Chris Sonnenday
- **HRSA Representatives**
  - Joyce Hager
  - Marilyn Levi
  - Jim Bowman
  - Melissa Greenwald
- **CDC Representatives**
  - Pallavi Annambhotla
  - Tonya Hayden
  - Jefferson Jones
- **OPTN/UNOS Staff**
  - Susan Tlusty
  - Cassandra Meekins
  - Gabe Vece
  - Amber Wilk
  - Michelle Wilson
  - James Alcorn
  - Tory Boffo
  - Kate Breitbeil
  - Leigh Kades
  - Leah Slife
  - Heather Stocker
  - Emily Womble
  - Ellie Willard
  - Anne Paschke