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Pediatrics & Donor Derived Disease Transmission: The US OPTN Experience

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Abstract

Potential donor-derived disease transmission events (PDDTE) are tracked by the OPTN Ad Hoc Disease Transmission Advisory Committee (DTAC). Specific evaluation of potential transmissions from pediatric deceased donors or the impact of donor derived disease transmissions to pediatric organ recipients has not been previously undertaken.

Methods: PDDTE reported to the DTAC between 2008-2013 were reviewed, characterized as proven, probable, possible, intervention without disease transmission (IWDT), unlikely, or excluded for both the whole event and for each individual recipient. Pediatric donors & recipients were defined as being 0-17 years of age. Analysis was undertaken to characterize potential disease transmission from pediatric donors to adult or pediatric recipients, and also to evaluate potential transmission from all donors to pediatric recipients. Proven and Probable (P/P) cases were further analyzed.

Results: 5,238 pediatric deceased U.S. donors accounted for 17,456 organ transplants during the study period. 103 PDDTE reports arose from these donors (2.0%). PDDTE were characterized as P/P (15%), possible (13%), IWDT (9%), unlikely and excluded (63%). Disease was transmitted to 22 of 54 potentially exposed (adult and pediatric) recipients with 6 attributable deaths. An infectious pathogen accounted for 13/15 of the P/P PDDTE associated with pediatric donors, affecting 19/50 potentially exposed recipients resulting in 5 deaths. 4 separate viral pathogens from six donors accounted for P/P transmissions to 11 recipients with the unanticipated transmission of CMV most common. No pediatric donor

transmitted HIV, HBV or HCV. Bacteria, fungi and parasites accounted for 3 (all staphylococci), 3 (Zygomycetes & Histoplasma) and 2 (both Toxoplasma) P/P transmissions from 7 donors, respectively. From the recipient side, 11/11,188 pediatric recipient deceased and living donor transplants during the study period were associated with a P/P PDDTE (< 0.1%) with infectious pathogens accounting for 9/11 P/P events. Infections were split amongst pathogen categories (bacteria 2, viruses 3, parasites 3 and fungi 1).

Conclusions: Reporting rates of PDDTE involving pediatric donors were very low and similar to rates from all donors, with resulting P/P transmissions occurring in only 0.1% of exposed recipients but transmissions were associated with 6 deaths. Rates of P/P transmission to pediatric recipients from any donor (< 0.1%) were also very low and similar to that of all recipients. Additional studies are needed to compare the pattern and outcome of donor-derived disease transmission from and to pediatric and adult donor and recipients.

Introduction

The United Network for Organ Sharing (UNOS) is the private, non-profit organization that manages the United States' organ transplant system under the Organ Procurement Transplant Network (OPTN) contract with HRSA. Since 2005, OPTN policy has required reporting of all unanticipated potential donor derived disease transmission events (PDDTE) in support of efforts to track, understand, and learn from donor derived disease transmission events in the United States.[1] Since 2008, reported PDDTE have been reviewed by the OPTN Ad Hoc Disease Transmission Advisory Committee (DTAC).[2] Since that time, the DTAC has worked to learn from this experience to enhance the transplant community's understanding of donor derived diseases and continually refine OPTN policies requiring reporting of PDDTE and communication between Organ Procurement Organizations (OPOs) and transplant centers. While a growing number of publications and guidance documents have been generated through ongoing efforts to learn from this experience, neither the specific evaluation of potential transmissions from pediatric donors nor the impact of donor derived disease transmissions on pediatric organ recipients has been previously undertaken. The current study was carried out to address these issues.

Methods

This study used data from the Organ Procurement and Transplantation Network (OPTN). The OPTN data system includes data on all donors, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere. The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN contractor. OPTN policy requires reporting of unexpected PDDTE to its Improving Patient Safety port (housed with UNet[SM] by either transplant hospitals or the organ procurement organizations (OPOs).[3] Once submitted, potential transmission events are initially screened by OPTN staff and additional details sought before undergoing formal review by the full DTAC following previously published processes and procedures[4]. For each reported PDDTE, the DTAC assessed the likelihood that transmission had occurred as either proven, probable, possible, unlikely, excluded, or intervention without disease transmission (IWDT) (typically an antimicrobial being given to prevent development of infection) for all recipients of a given donor.[4] The committee's assessment for potential event included an overall assessment for a PDDTE based on the highest level (e.g. proven versus possible) assigned to any of the potentially exposed recipients (e.g. if one recipient experienced a proven transmission the overall assessment would be proven regardless of the outcome for other recipients) as well as providing individual assessments for all recipients. Once all individual recipient assessments and the overall assessment were assigned for each PDDTE, this information was recorded in the OPTN DTAC database.

All cases reported to and assessed by the DTAC between 2008 and 2013 were included in this review. Potential pediatric cases were defined as involving either a donor or recipient less than 18 years of age. The DTAC database was reviewed to identify PDDTE involving a pediatric deceased donor of organs to adult or pediatric recipients as well as cases involving any age donor to pediatric recipients. All PDDTE were considered within the confines of confidential medical peer review. Because of this, the DTAC is not permitted to provide specific details for any given single potential transmission event or to provide details for any disease type where only a single report was received during the year. PDDTE classified as either proven or probable as well as those categorized as unlikely or excluded were combined for the purpose of analysis.

Results

An overview of donor derived disease from pediatric donors to all recipients is summarized in Figure 1. A total of 5,238 pediatric deceased donors accounted for 17,456 organ transplants during the study period with 11,393 going to adult recipients and 6,064 to children. 103 PDDTE reports were submitted to the OPTN Improving Patient Safety Portal involving these donors (2%). The overall evaluation by the DTAC classified 15 of these PDDTE as proven/probable for an overall rate of 0.3% of pediatric donors being associated with a proven/probable donor-derived disease transmission event. Of the remaining PDDTE, 13 were assessed to be possible, 9 to be IWDT, and 66 to be unlikely/excluded. The 15 proven/probable cases were assessed as resulting in transmission to 22 of 54 total (both pediatric and adult) exposed recipients which represents transmission to 0.1% of all transplant recipients with pediatric organs. Infections accounted for 13/15 proven/probable PDDTE; transmission of a malignancy and a peanut allergy accounted for the remaining 2 proven/probable events. As summarized in Figure 1, viral infections were the most commonly transmitted class of pathogens affecting 11 recipients from 6 donors. Cytomegalovirus (CMV) was the most commonly transmitted virus accounting affecting 4 recipients from 3 donors. Two of the donors were teenagers while the other donor was younger. CMV would be considered an unanticipated PDDTE in situations where both the donor and recipient pre-transplant serologies were negative. Despite 277 pediatric deceased donors identified as PHS increased risk during the period, no transmissions involving Hepatitis (B or C) or HIV from a pediatric donor occurred during the study period. Bacteria, fungi and parasites accounted for 3 (all staphylococci), 2 (Zygomycetes and Histoplasma) and 2 (both toxoplasma) donor transmissions, respectively. Disease transmission was assessed as causing 6 deaths in 2 pediatric and 4 adult recipients. Five of the deaths were attributed to transmission of an infectious pathogen from 4 donors (Toxoplasma, Zygomycetes, Balamuthia, and LCMV) and 1 death was due to transmission of a malignancy, resulting in an attributable death rate due to a donor-derived transmission event of 0.03% of all transplant recipients of pediatric organs.

A summary of donor derived disease occurring in pediatric recipients from any donor is shown in Figure 2. A total of 11,188 children received an organ from either an adult or pediatric donor during the study period. Eleven pediatric organ recipients experienced a proven/probable PDDTE (0.1%) with infectious pathogens accounting for 9/11 of the proven/probable transmission events. Infections were evenly split amongst pathogen categories (viruses 3, bacteria 2, parasites 3 and fungi 1) with 8 different pathogens accounting for the 9 proven/probable infectious transmissions. Pathogens specifically associated with transmission included CMV, HBV, HTLV2, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*, Strongyloides, Toxoplasma (2 separate donors to 2 recipients), and

Histoplasmosis. The remaining two proven/probable PDDTE were attributable to a malignancy and a peanut allergy. Proven/probable PPDTE occurred in 5 liver recipients (2 bacterial and 2 viral infection as well as the peanut allergy), 4 heart recipients (1 viral, 1 fungal and 2 parasites), 2 lung recipients (1 fungal infection and 1 malignancy) and 1 kidney recipient (parasitic infection). Overall, proven/probable transmission events accounted for two deaths in pediatric recipients for an attributable death rate of 0.02% of all pediatric organ recipients during the study period. Of note, these two fatal transmissions were the two fatal transmission cases noted from pediatric donors.

Discussion

The importance of the donor as a source of infection in organ recipients was recognized early in the history of transplantation. Seminal observations of the critical role of the donor as a major source of cytomegalovirus and Epstein Barr Virus eventually led to the recognition of a distinction between anticipated (for which one could potentially develop preventive strategies against and at a minimum provide specific consul to organ recipients and their family about the presence of risk) and unanticipated donor derived infections. Additional observations also identified the potential for transmission of malignancies and even allergies from the donor to one of more recipients. As occurrences of high profile donor-derived transmissions of pathogens including HIV[5], HCV[5], rabies[6] and West Nile Virus[7,8] were reported, the need for systematic tracking of potential donor derived infections and other donor derived diseases became increasingly recognized. In the USA, this was accomplished through mandated reporting of PDDTE to the OPTN and the creation of the OPTN Ad Hoc Disease Transmission Advisory Committee and the development of its now well established processes and infrastructure. Additional efforts have been initiated by a number of individual countries and by the World Health Organization (Project NOTIFY).[9] Taken together, these efforts share a common goal of enhancing the safety of transplant recipients through a better understanding of potential risks for disease transmission and have resulted in the enhanced awareness of the transplant community of the importance of the potential for and clinical consequences of donor-derived disease transmission, informing changes in both policy and the clinical practice of transplantation. However, while disease transmission events involving pediatric donors and pediatric recipients have been included in prior aggregate analyses, specific evaluation for unique characteristics of disease derived from pediatric donors or spectrum and impact of donor derived disease on pediatric recipients has not been previously studied. Accordingly, the

results of the current study are both informative and reassuring in that the incidence and outcome of donor derived disease transmission events appear to be similar when one compares both pediatric and adult donors and recipients.

The results of the current study identified that reported rates of PDDTE involving pediatric donors were very low (2%) with proven/probable transmissions from pediatric donors occurring in only 0.1% of recipients (either adult or pediatric). The cumulative incidence rate of reported PDDTE was 1.9% for deceased donors (adult and pediatric) reported to the OPTN through 2013 involving donors recovered in 2008-2012 though the overall rate for all donors (deceased and living) was 1.1%.[4] The rate of proven/probable transmission during this time period was 0.4% and 0.2% from deceased donors (adult and pediatric) and all donors (living and deceased), respectively.[4] As children are rarely if ever used as living donors, comparison of both the rate of PDDTE reporting and of proven/probable transmission between pediatric and all deceased donors would seem most appropriate. Based upon these comparisons, the current results suggest that rates of both reporting a potential PDDTE and of a proven/probable transmission were similar for pediatric and adult deceased donors during this time period.

Five Proven/Probable disease transmission events from a pediatric donor were assessed as causing 6 deaths (two in pediatric and four in adult recipients) in this study for an attributable mortality rate of 0.03% of all recipients of pediatric organs. Five of the six deaths were associated with the transmission of an infectious pathogen and one was due to transmission of a malignancy. Two pediatric recipients were assessed as dying secondary to a donor derived transmission (both from pediatric donors) for an attributable mortality rate of 0.02%. In comparison, analysis of proven/probable disease transmission from all deceased donors (adult and pediatric) during this time period identified 39 deaths affecting the 110,402 recipients transplanted for an attributable mortality rate of 0.04%. Accordingly, rates of attributable mortality due to proven/probable disease transmission appear to be similar in both the adult and pediatric donor and recipient populations.

Infectious pathogens accounted for 13 of 15 (87%) of proven/probable donor derived transmission events from pediatric donors during this study period. Viral pathogens accounted 46% of these transmissions but important transmission events also occurred due to bacteria, fungi and parasites. In comparison, in a cohort including all donors (but largely adult donors) viral infections accounted for 42 of 219 (19%) of transmission with 19 hepatitis C or hepatitis B transmissions, pathogens not transmitted from our pediatric cohort

despite the fact that it included 277 donors identified as PHS increased risk. Further malignancies and non-infectious events, accounted for the largest percentage of adult donor transmission events (30%) and the largest number of fatal donor transmissions, but were very uncommon in the pediatric population.[10]

Limitations include the reliance of all recipient centers and OPOs to report suspected donor derived diseases for review through what is a passive reporting system. In addition the data for the DTAC members to review are limited to deidentified information with follow-up generally confined to 45 days after the event. Accordingly, some cases may have been either under or overclassified.

In summary, reported rates of PDDTE involving pediatric donors were very low and similar to rates from all donors, with resulting P/P transmissions occurring in only 0.1% of exposed recipients but transmissions were associated with 6 deaths. Rates of P/P transmission to pediatric recipients from any donor (< 0.1%) were also very low and similar to that of all recipients. Additional studies are needed to compare the pattern and outcome of donor derived disease transmission from and to pediatric and adult donor and recipients.

Acknowledgement

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Figure 1. Donor Derived Disease from Pediatric Donors: 2008-2013

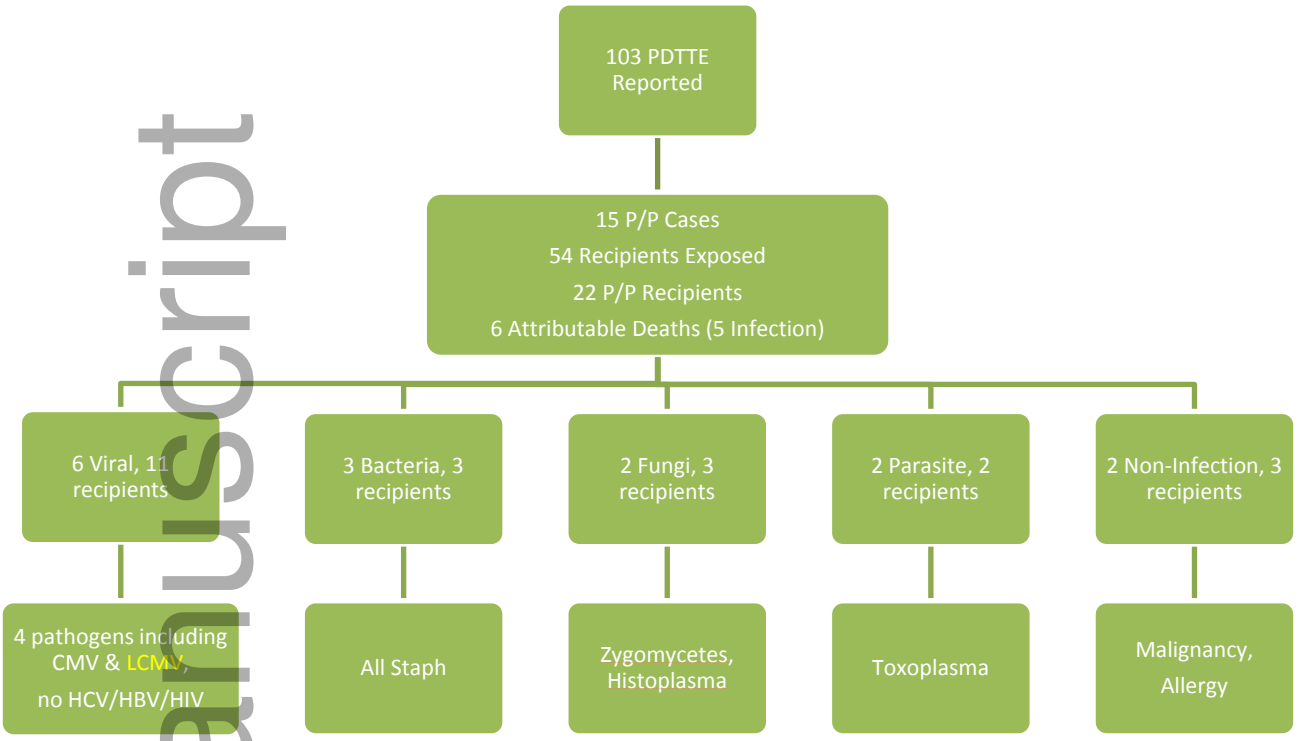

Figure 2: Donor Derived Disease to Pediatric Recipients: 2008-2013