Original Investigation

Potential and Actual Neonatal Organ and Tissue Donation After Circulatory Determination of Death

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IMPORTANCE The need for transplants continues to exceed organ and tissue donor availability. Although recent surgical advances have resulted in successful transplants using very small pediatric donors, including neonates, the actual practice of neonatal organ donation after circulatory determination of death (DCDD) remains uncommon.

OBJECTIVE To describe the percentage of neonates potentially eligible for DCDD, including those who underwent successful donation, and reasons for ineligibility in those who did not in a single neonatal intensive care unit (NICU).

DESIGN, SETTING, AND PARTICIPANTS We obtained data from the Children's Hospital Neonatal Database and Intermountain Donor Services (IDS) organ procurement records. The 136 deaths that occurred in the NICU of the Primary Children's Hospital, Salt Lake City, Utah, from January 1, 2010, through May 7, 2013, were reviewed retrospectively from January 12 through July 1, 2014, to determine potential eligibility for DCDD as determined by IDS minimum eligibility criteria (requirement of life-sustaining interventions and weight >2 kg). For patients who did not undergo DCDD, we reviewed records to determine the reasons for ineligibility.

MAIN OUTCOMES AND MEASURES Potential eligibility for DCDD among neonates who died in the study NICU.

RESULTS Of 136 deaths in the NICU, 60 (44.1%) met criteria for DCDD; however, fewer than 10% were referred appropriately to the regional organ procurement organization for evaluation. Forty-five neonates (33.1%) ultimately died within 90 minutes of withdrawal of life-sustaining interventions and thus would have been eligible for organ donation based on warm ischemic time. The most common causes of death among the 60 potentially eligible neonatal donors were neonatal encephalopathy (n = 17) and multiple congenital anomalies (n = 14). Nonreferral or late referral by the medical team was the most frequent reason for donor ineligibility, including 49 neonates (36.0%). Overall, only 4 neonates (2.9%) underwent successful DCDD.

CONCLUSIONS AND RELEVANCE Although almost half of all neonatal deaths identified met minimum IDS criteria, most of these patients were not referred or were referred too late for evaluation. Although small size remains the primary reason for exclusion from DCDD, improved education with regard to criteria and the importance of timely referral by neonatologists and other members of the NICU team would likely result in a significant increase of future donations.

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n the past, neonates have not been eligible for organ donation owing to the technical difficulties and the high risk for graft complication involved with transplant of their small organs.1-4 Donation after neurologic determination of death occurs while optimal organ perfusion is maintained by continued medical therapies to the time of organ recovery. Despite established criteria for the diagnosis of death by neurologic criteria in term neonates, organ and tissue donation after neurologic determination of death rarely occurs in this population.5-7 At present, fewer than 1% of all organ or tissue donations come from donors younger than 1 year.8 However, ongoing organ shortages coupled with improved technology and surgical techniques have led to a renewed interest in neonates as potential candidates for organ donation after circulatory determination of death (DCDD).9

Donation after circulatory determination of death occurs in cases of severe life-limiting illness after a decision is made to withdraw life-sustaining interventions and allow death to occur. The period from withdrawal of these interventions to the time of death is termed warm ischemic time (WIT) and must be relatively short for successful DCDD. Many critically ill neonates die in the neonatal intensive care unit (NICU) after withdrawal of life-sustaining interventions, but organ donation is frequently not considered before this time, resulting in a missed opportunity for DCDD. Unfortunately, these missed opportunities are not unique to neonates.13,14

Although most DCDD has occurred in adults, pediatric donors increasingly undergo DCDD, including neonates.15 At Primary Children’s Hospital, Salt Lake City, Utah, a number of neonates have been successfully referred for DCDD and have donated en bloc kidneys for transplant in older patients.3-4 Recent studies have shown that en bloc pediatric kidney transplants have clinical outcomes similar to those of size-matched recipients of single adult kidneys.16-18 Given this experience, we hypothesized that many neonates who die in the NICU could serve as organ and/or tissue donors if appropriately identified and if their families are counseled regarding the opportunity to participate in DCDD.

### Methods

To determine the percentage of deaths of neonates eligible for DCDD, we performed a retrospective analysis of deaths in our NICU from January 1, 2010, through May 7, 2013. We reviewed the frequency with which neonates underwent evaluation for DCDD and whether organ donation was successfully completed. For neonates in whom DCDD did not occur, we reviewed records to determine the reasons for ineligibility.

Primary Children’s Hospital, an Intermountain Healthcare facility, operates a large level IV referral NICU serving patients in the Mountain West region. Intermountain Donor Services (IDS) is the regional organ procurement organization (OPO) and has provided the opportunity for DCDD in pediatric donors as small as 2 kg since 2010. We reviewed the records of neonates who died in the hospital during the study period. Although patients ranged in age from less than 1 day to 1 year, for simplicity we have used the term neonate to describe all these patients. Deidentified data were collected prospectively on all admissions as part of the Children’s Hospital Neonatal Database for which Primary Children’s Hospital is a member. The institutional review board for Primary Children’s Hospital approved this study and waived the need for informed consent for medical record review.

### Potential Eligibility for Organ Donation

Deaths were reviewed from January 12 through July 1, 2014, to determine potential eligibility for organ/tissue donation as per ODS criteria. Evaluation of criteria for neurologic determination of death was performed when deemed appropriate by the attending physician. Minimum inclusion criteria for DCDD include a weight exceeding 2 kg, reliance on life-sustaining medical interventions, and a WIT of less than 90 minutes. Although additional exclusions to donation may apply (eg, bacteremia, renal anomalies), these exclusions are not considered by IDS to be absolute. Patients must be identified and referred to the OPO before withdrawal of life-sustaining interventions to allow for evaluation, preparation, and monitoring. For the purpose of this study, a referral made before withdrawal of these interventions was considered a timely referral, and any referral after withdrawal or any failure to refer was considered a late referral. For small (patient weight, 2-5 kg) pediatric DCDD, IDS currently provides the possibility of en bloc renal transplant, hepatocyte donation, and heart valve transplant (Figure). When minimum eligibility criteria are met and timely OPO referral is made, the transplant surgeon and IDS review each case and determine final eligibility for donation.

### Review of OPO Referrals

In addition to records from the Children’s Hospital Neonatal Database, we reviewed OPO records to determine whether donation occurred and the reasons for ineligibility (if applicable). Demographic characteristics (eg, gestational age, weight, and cause of death) were evaluated between neonates with timely and late OPO referrals. The last measured aspartate transaminase, alanine transaminase, and creatinine concentrations were analyzed as surrogate markers of liver and kidney function at the time of death. In neonates with known chromosomal abnormalities or major defects involving 2 or more organ systems, these were evaluated together as multiple anomalies.
**Statistical Analysis**

Characteristics of potential DCDD candidates were summarized using median (interquartile range) data and counts depending on variable distributions. Summaries were stratified by timely and late OPO referrals. We compared the cause of death across OPO referral timeliness using a Fisher exact test and continuous variables using an exact Wilcoxon rank sum test. Statistical analysis was conducted using R (version 3.0.3 [http://www.r-project.org]). Significance was defined as \( P < .05 \).

**Results**

**Study Cohort**

One hundred thirty-six deaths occurred during the study period. Of these, 76 neonates (55.9%) weighed more than 2 kg (60 [44.1%] did not meet weight criteria). Weight in 57 neonates (41.9%) exceeded 2.74 kg, making them eligible for heart valve donation. Eleven deaths (8.1%) occurred despite continued medical care (without withdrawal of life-sustaining interventions). Of the 65 neonates (47.8%) who had withdrawal of life-sustaining interventions, 5 (3.7%) had life-limiting illnesses without significant respiratory disease (ie, no requirement of mechanical ventilation), which made these neonates ineligible. Of the 60 remaining neonates eligible for DCDD, 45 (33.1%) died within 90 minutes of withdrawal of life-sustaining interventions, meeting WIT criteria for en bloc kidney and hepatocyte donation. Seven neonates (5.1%) exceeded the WIT, precluding organ donation, and 8 (5.9%) had a WIT of 90 to 180 minutes, making them eligible for hepatocyte donation. Only 4 neonates (2.9%) underwent organ or tis-
Table. OPO Referral in Patients Weighing Greater Than 2 kg

<table>
<thead>
<tr>
<th>Variable</th>
<th>OPO Referral</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Timely (n = 11)</td>
<td>Late (n = 49)</td>
</tr>
<tr>
<td>Weight, median (IRQ), kg</td>
<td>3.5 (3.3–3.5)</td>
<td>3.2 (2.8–4)</td>
</tr>
<tr>
<td>Cause of death, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>0</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Idiopathic hydrops</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Multiple congenital anomalies</td>
<td>3 (27)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Neonatal encephalopathy</td>
<td>5 (45)</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Neuromuscular disease (excluding encephalopathy)</td>
<td>2 (18)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Persistent pulmonary hypertension of the newborn</td>
<td>0</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Pulmonary hypoplasia (including congenital diaphragmatic hernia)</td>
<td>0</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Skeletal dysplasia</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Total intestinal aganglionosis</td>
<td>1 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Warm ischemic time, median (IRQ), min</td>
<td>43.8 (34.5–220.5)</td>
<td>48 (22.8–90.0)</td>
</tr>
<tr>
<td>AST level, median (IRQ), U/L</td>
<td>43 (17.0–83.8)</td>
<td>32 (23.0–57.0)</td>
</tr>
<tr>
<td>ALT level, median (IRQ), U/L</td>
<td>49 (32.5–74.2)</td>
<td>65 (38.0–127.0)</td>
</tr>
<tr>
<td>Creatinine level, median (IQ), mg/dL</td>
<td>0.4 (0.2–0.6)</td>
<td>0.6 (0.4–1.1)</td>
</tr>
<tr>
<td>Gestational age at death, median (IRQ), wk</td>
<td>41.1 (37.8–43.9)</td>
<td>39.0 (37.6–41.3)</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; IQR, interquartile range; OPO, organ procurement organization.

SI conversion factors: To convert ALT and AST to microkatal per liter, multiply by 0.0167; creatinine to micromoles per liter, multiply by 88.4.

<sup>a</sup> Values were missing for AST levels in 3 patients in the timely referral group; for ALT levels in 3 patients in the timely referral group and 8 in the late referral group; and for creatinine levels in 1 patient in the timely referral group and 3 in the late referral group.

<sup>b</sup> Median (IQR) data are reported for all continuous variables owing to skewed distributions, and they were analyzed using exact Wilcoxon rank sum tests. Primary diagnosis was analyzed using a Fisher exact test.

OPO Referral

Sixty neonates had withdrawal of life-sustaining interventions and weighed more than 2 kg, thereby meeting criteria for referral to the OPO. Only 11 neonates (8.1%) had timely referral; in all 11 cases, medical records indicated that the family inquired about and actively pursued organ donation. Of the timely OPO referrals, 4 neonates were ineligible on further evaluation by the OPO (3 had congenital anomalies and 1 had total intestinal aganglionosis and did not require mechanical ventilation for life support), 4 families declined further participation in the DCDD process, and 3 neonates donated en bloc kidneys. Forty-nine neonates (36.0%) had late OPO referral. Of these, 26 neonates were referred before their death but after withdrawal of life-sustaining interventions, making them ineligible. One neonate donated heart valves at the time of autopsy despite being referred too late for organ donation.

We found that more than one-third of all NICU deaths met the minimum criteria for DCDD. Of these, only a small percentage were identified and referred to the OPO early enough to undergo evaluation for DCDD. Although our sample size was small, our DCDD rate for timely referral of neonates was 3 of 11 neonates (27%). Assuming a similar rate for all deaths meeting minimum criteria, we estimate that as many as 4.7 neonatal organ/tissue donations per year (approximately 12% of all deaths) could occur from our single-center NICU population. This estimate is about 5.4-fold greater than our current rate of 0.86 donations per year. We may have underestimated the potential organ donors given that previously published rates of pediatric donor consent range from 40% to 70%.<sup>19</sup>

Supporting Studies

Our findings support those of several recent studies looking at the potential for neonatal DCDD. Labrecque et al<sup>24</sup> estimated that 8% of all neonatal deaths in 3 Harvard Program in Neonatology NICUs were eligible for DCDD. Labrecque et al used stricter criteria (weight threshold, 3 kg; WIT, 30 minutes) and concluded that significant potential for neonatal organ donation exists. They estimated that 14 livers, 18 kidneys, and 10 hearts could have been transplanted from their
3-year review of nearly 200 neonatal deaths. Hanley et al also evaluated the potential for kidney donation among neonates with similar DCDD criteria to those of our study. In their retrospective review of potential DCDD candidates weighing more than 1.8 kg and with a WIT of less than 120 minutes in their NICU population, Hanley et al determined that as many as 4.0 organ donations per year were possible. They estimated that 487 to 1145 paired donor kidneys annually in the United States could come from DCDD programs in NICUs. Although the number of potential neonatal organ donors varies based on the criteria used, our study, in addition to those of Labrecque et al and Hanley et al, suggests that the projected contribution of donor kidneys may be equivalent to or even exceed projections from broad implementation of DCDD programs in pediatric ICUs.

The minimum weight and WIT thresholds for successful DCDD are subject to debate and vary among OPOs. Published reports (using the definition of WIT as the time from extubation to initiation of cold perfusion) suggest that the optimal WIT is less than 60 minutes for kidney transplants. In addition to WIT criteria, greater donor weight and height have been associated with an improved rate of kidney recovery. However, graft survival is being achieved with donors as small as 1.9 kg, and many OPOs are accepting WIT ranging from 90 to 120 minutes with good results. In addition to variation in minimum weight and WIT among programs, the period after declaration of death but before initiation of the procurement operation varies. The Institute of Medicine has stated that the time should be no shorter than 2 minutes to ensure that autoresuscitation does not occur, but no longer than 5 minutes. Standardized DCDD protocols in small infants and children are needed because the practice varies nationally.

Potential Neonatal Contribution to the Donor Pool

Neonatal kidneys are almost always transplanted into adult recipients. The grafts grow with time and have good results in adults. Larger donor weight and shorter WIT may provide for potential liver, lung, intestine, and even heart DCDD in the appropriately defined, size-matched pediatric population. However, the number of small pediatric patients on transplant waiting lists is small compared with the more than 100 000 adults on the kidney transplant waiting list.

Although nearly half of all neonatal deaths identified in our study population met criteria for OPO referral, fewer than 10% were referred before withdrawal of life-sustaining interventions. Inadequate weight has been the primary reason for exclusion of neonates from participation in DCDD. This study is, to our knowledge, the first to identify inadequate OPO referral by health care practitioners as an important hurdle to neonatal participation in organ donation. Although specific reasons for late OPO referral could not be assessed in our study, similar problems with identification and timely referral in adult and older pediatric populations have been well described. Hospitals have worked to better recognize imminent death, and many have instituted clinical referral triggers to optimize timely OPO referrals. However, clinical triggers or scoring tools specific to the unique developmental limitations of neonates have not yet been established.

Even in large academic centers with active transplant programs, many physicians have limited understanding of the OPO guidelines. We speculate that many practitioners in the NICU have misconceptions about organ donation, lack of familiarity with the DCDD process, and relatively little experience with counseling families to discuss organ donation. In addition, practitioners are likely unaware of recent advances in neonatal kidney transplantation and/or rely on outdated donation criteria. In our study, we identified a family’s request as a critical step for timely OPO referral, suggesting that organ donation is unlikely to occur in our NICU unless the family initiates the process.

Outcomes of Transplanted Neonatal Organs, Cells, and Tissues

Because of the size of kidneys from small pediatric donors (weight <5 kg), outcomes are improved when these kidneys are transplanted en bloc. Despite a slightly higher risk for graft thrombosis, successful kidney transplant has occurred from donors as small as 1.9 kg. En bloc kidneys from small pediatric donors have similar rates of graft survival and function compared with those from larger traditional donors and superior outcomes compared with those from deceased expanded criteria donors. Although most small pediatric kidneys are allocated to adults, children are likely to benefit from improved use of neonatal kidneys. Short-term follow-up of small pediatric kidneys transplanted to pediatric recipients has shown similar good outcomes.

Another potential benefit of early referral and evaluation of the neonatal population for potential donation is the possibility of hepatocyte donation. CytoNet, LLC processes donated livers and isolates hepatocytes that are infused into the portal vein of infants with congenital urea cycle defects as a bridge to transplant. Clinical trials of this technology are currently under way.

Potential DCDD Identification and OPO Referral in Neonates

Although the timeliness of OPO referral may vary, it must occur before the withdrawal of life-sustaining interventions. Intermountain Donor Services has optimized their approach to mobilizing resources for rapid DCDD and has achieved successful DCDD within 90 minutes of referral. In the 3 cases of successful kidney donation in our study, IDS referral occurred 3 hours 14 minutes, 1 hour 25 minutes, and 19 hours 6 minutes before the withdrawal of life-sustaining interventions.

In pediatric ICUs, certain factors have been identified as being associated with higher participation in organ donation, including the presence of a level I trauma program or pediatric critical care medicine fellowship program. In addition, parental exposure to information about organ donation before their child’s death, the allotment of sufficient time to discuss organ donation before withdrawal of life-sustaining interventions, and the active involvement of a practitioner from the child’s health care team are associated with increased participation in organ donation. On the other hand, a lack of confidence in the donation process, misperceptions of cultural viewpoints on organ donation, and concern about differing
medical care for donors are all cited as reasons for nonparticipation.44 We suspect that more consistent, timely discussion with families about organ donation when their newborn’s death is imminent will likely increase participation and improve the end-of-life experience for families who can find comfort in allowing their child to give life to others.

Although one-third of the deaths in our study met the minimum criteria for potential DCDD, meeting a minimum weight threshold and WIT does not equate to successful organ transplants. End-organ function, coexisting conditions (eg, syndromes, sepsis), family wishes, and surgeon availability all affect the number of potential candidates who actually become donors. At present, only a single center (University of California, Davis) of which we are aware accepts kidney donations from donors as small as 2 kg. Despite the lack of resources, transplant surgeon availability has not been a limiting factor in DCDD participation for our population to date. However, a scarcity of additional referral sites for neonatal donors will become problematic if OPO referrals increase and more NICUs begin to participate in DCDD without a coexisting increase in surgical expertise and transplant centers willing to use neonatal organs. Until consistent, timely OPO referral occurs throughout multiple NICUs in multiple regions, the true potential and challenges of neonatal organ donation can only be speculated.

Study Limitations
This study is limited by its retrospective nature and the experience of a single center. Our level IV referral NICU has a high rate of medical complexity and acuity that may limit translation of our findings to other centers. In addition, OPO referral was the only available measure to assess consideration of organ donation for any given patient. In some cases, OPO referral may have occurred late because organ donation was discussed and the families declined participation. Although we did not find a difference in most patient characteristics between timely and late referrals, our sample size was small and therefore may not have detected some clinically important differences. We noted an overall higher median creatinine level in the late referral group, including 2 neonates with intrinsic kidney disease. Although this variable may have contributed to a lower OPO referral rate in our study, the absolute creatinine level is not the sole determinant of transplant eligibility. Higher creatinine levels should not preclude OPO referral because kidneys tend to recover after transplant, even in the setting of acute kidney injury in the donor.

Additional Considerations
Neonatal DCDD invokes unique ethical and emotional responses that have been described previously.45 Health care practitioners must have a better understanding of the process of DCDD and adequately communicate this information with families. Families wishing to participate in DCDD must realize that the death environment in the NICU will be altered once their child undergoes withdrawal of life-sustaining interventions. Their child will require continued invasive monitoring after withdrawal of the interventions, and the immediacy of the organ recovery process will limit the amount of time they have to spend with their dying child. Throughout this process, the medical and transplant teams must realize that the child and family need to remain the priority. Although pediatric (including neonatal) DCDD has unique ethical considerations, a recent American Academy of Pediatric Bioethics Policy Statement has supported the entire process, emphasizing that organ donation should be undertaken in an ethiclly rigorous manner.46 We believe that part of this ethical rigor should involve an evaluation of our current assumptions about ineligibility and the neonatologist’s role in providing equipoise in end-of-life decisions regardless of a family’s knowledge of (or request to participate in) organ donation.

Conclusions
We found that many neonates who die in the NICU would be eligible to participate in DCDD. Application of these results to other NICUs with similar populations could increase organ and tissue donation substantially and on a national level at a time of progressively increasing transplant wait lists among children and adults. At present, a significant disconnect exists between donor potential and the identification and timely OPO referral that ultimately lead to successful transplants. Improved education of NICU practitioners and staff regarding the process of OPO referral will likely improve the potential opportunities for families to participate in organ donation.

REFERENCE
Neonatal Organ Tissue Donation After Circulatory Determination of Death

Original Investigation Research


