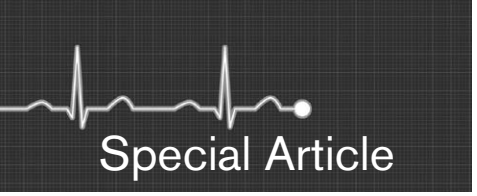

Management of the Potential Organ Donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations Consensus Statement

Robert M. Kotloff, MD[1]; Sandralee Blosser, MD[2]; Gerard J. Fulda, MD[3]; Darren Malinoski, MD[4]; Vivek N. Ahya, MD[5]; Luis Angel, MD[6]; Matthew C. Byrnes, MD[7]; Michael A. DeVita, MD[8]; Thomas E. Grissom, MD[9]; Scott D. Halpern, MD[5]; Thomas A. Nakagawa, MD[10]; Peter G. Stock, MD[11]; Debra L. Sudan, MD[12]; Kenneth E. Wood, DO[13]; Sergio J. Anillo, MD[14]; Thomas P. Bleck, MD[15]; Elling E. Eidbo, MBA[16]; Richard A. Fowler, MBA[16]; Alexandra K. Glazier, JD, MPH[17]; Cynthia Gries, MD[18]; Richard Hasz, MFS, CPTC[19]; Dan Herr, MD[20]; Akhtar Khan, MD[21]; David Landsberg, MD[22]; Daniel J. Lebovitz, MD[23]; Deborah Jo Levine, MD[6]; Mudit Mathur, MD[24]; Priyumvada Naik, MD[25]; Claus U. Niemann, MD[11]; David R. Nunley, MD[26]; Kevin J. O'Connor, MS[27]; Shawn J. Pelletier, MD[28]; Omar Rahman, MD[29]; Dinesh Ranjan, MD[30]; Ali Salim, MD[31]; Robert G. Sawyer, MD[28]; Teresa Shafer, RN, MSN[32]; David Sonneti, MD[33]; Peter Spiro, MD[34]; Maryam Valapour, MD[1]; Deepak Vikraman-Sushama, MD[12]; Timothy P. M. Whelan, MD[35]; for the Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations Donor Management Task Force

Abstract: This document was developed through the collaborative efforts of the Society of Critical Care Medicine, the American College of Chest Physicians, and the Association of Organ Procurement Organizations. Under the auspices of these societies, a multidisciplinary, multi-institutional task force was convened, incorporating expertise in critical care medicine, organ donor management, and transplantation. Members of the task force were divided into 13 subcommittees, each focused on one of the following general or organ-specific areas: death determination using neurologic criteria, donation after circulatory death determination, authorization process, general contraindications to donation, hemodynamic management, endocrine dysfunction and hormone replacement therapy, pediatric donor management, cardiac donation, lung donation, liver donation, kidney donation, small bowel donation, and pancreas donation. Subcommittees were charged with generating a series of management-related questions related to their topic. For each question, subcommittees provided a summary of relevant literature and specific recommendations. The specific recommendations were approved by all members of the task force and then assembled into a complete document. Because the available literature was overwhelmingly comprised of observational studies and case series, representing low-quality evidence, a decision was made that the document would assume the form of a consensus statement rather than a formally graded guideline. The goal of this document is to provide critical care practitioners with essential information and practical recommendations related to management of the potential organ donor, based on the available literature and expert consensus. (*Crit Care Med* 2015; 43:1291–1325)

Key Words: critical care; organ donor; organ transplantation

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As of December 2013, over 120,000 patients comprised the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) waiting list (1). In 2012, only 22,187 organ transplantations from 8,143 deceased donors were performed, and over 6,467 patients died while waiting for an available organ (1). This disparity between need and supply of transplantable organs is growing steadily in the United States, with the number of individuals on the waiting list far surpassing the number of available donors and organs. In addition to the obvious benefits to transplant recipients, the psychological and social benefits of organ donation for the potential donor and family are increasingly recognized (2). When the authorization process meets a Donation Service Area's

definition of effective requesting, authorization is obtained over 75% of the time (OPTN data, January 2008–June 2010), and approximately 46% of adults in the United States are registered to be an organ donor on a state registry (3), demonstrating the prevalent desire to donate organs. To respect and carry out these wishes, the Revised Uniform Anatomical Gift Act requires organ procurement organizations (OPOs) and donor hospitals to have the necessary policies and procedures in place to preserve the option of donation for every potential donor and their family (4). This includes avoiding a deceleration in the critical care provided

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The American College of Critical Care Medicine (ACCM), which honors individuals for their achievements and contributions to multidisciplinary critical care medicine, is the consultative body of the Society of Critical Care Medicine (SCCM) that possesses recognized expertise in the practice of critical care. The College has developed administrative guidelines and clinical practice parameters for the critical care practitioner. New guidelines and practice parameters are continually developed, and current ones are systematically reviewed and revised.

These guidelines have been reviewed and endorsed by the American Association of Critical Care Nurses, the American Society of Transplantation, and the United Network of Organ Sharing.

[1]Department of Pulmonary Medicine, Cleveland Clinic, Cleveland, OH.

[2]Division of Pulmonary, Allergy, and Critical Care Medicine, Penn State Hershey Medical Center, Hershey, PA, and Pittsburgh Critical Care Associates, Pittsburgh, PA.

[3]Department of Surgery, Christiana Care Health System, Newark, DE.

[4]Department of Surgery, Portland Veterans Affairs Medical Center, Portland, OR.

[5]Pulmonary, Allergy, and Critical Care Division, Hospital of the University of Pennsylvania, Philadelphia, PA.

[6]Division of Pulmonary Diseases and Critical Care Medicine, University of Texas Health Center at San Antonio, San Antonio, TX.

[7]Department of Surgery, University of Minnesota Medical Center, Minneapolis, MN.

[8]General Surgery Department, Harlem Hospital Center, New York, NY.

[9]Department of Anesthesiology, University of Maryland Medical Center, Baltimore, MD.

[10]Section of Pediatric Critical Care, Wake Forest Baptist Health Medical Center, Winston-Salem, NC.

[11]Department of Surgery, University of California, San Francisco, San Francisco, CA.

[12]Department of Surgery, Duke University Medical Center, Durham, NC.

[13]Geisinger Medical Center, Danville, PA.

[14]SUNY Buffalo, Buffalo, NY.

[15]Department of Neurology, Rush Medical College, Chicago, IL.

[16]Association of Organ Procurement Organizations, Vienna, VA.

[17]New England Organ Bank, Waltham, MA.

[18]Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA.

[19]Gift of Life, Philadelphia, PA.

[20]Department of Medicine, University of Maryland Medical Center, Baltimore, MD.

[21]Department of Surgery, Alleghany General Hospital, Pittsburgh, PA.

[22]Department of Emergency Medicine, SUNY Upstate Medical Center, Syracuse, NY.

[23]Department of Pediatric Critical Care Medicine, Akron Children's Hospital, Akron, OH.

[24]Department of Critical Care Medicine, Loma Linda University Children's Hospital, Loma Linda, CA.

[25]Intensivist, Atlanta, GA.

[26]Division of Pulmonary and Critical Care Medicine, University of Louisville Hospital, Louisville, KY.

[27]LifeCenter Northwest, Bellevue, WA.

[28]Department of Surgery, University of Virginia Health System, Charlottesville, VA.

[29]Pulmonary and Critical Care, Indiana University Health System, Indianapolis, IN.

[30]Department of Surgery, Oscar G. Johnson Veterans Administration Medical Center, Iron Mountain, MI.

[31]Trauma, Burns, and Surgical Critical Care Division, Brigham and Women's Hospital, Boston, MA.

[32]Texas Transplantation Society, Austin, TX.

[33]Division of Pulmonary and Critical Care Medicine, University of Wisconsin, Madison, WI.

[34]Pulmonary Department, Harlem Hospital, New York, NY.

[35]Division of Pulmonary, Critical Care, and Sleep Medicine, Medical University of South Carolina, Charleston, SC.

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For information regarding this article, E-mail: kotlofr@ccf.org

to patients with catastrophic brain injuries until organ donation has been discussed in an appropriate manner (4).

The majority of transplanted organs come from donors after neurologic determination of death (previously termed "brain death"). Because all of these donors enter the ICU at some point during treatment, intensivists are often involved in their care. Following catastrophic brain injury, with the determination of futility of care, the intensivist's goals shift from optimizing cerebral perfusion pressure to maintaining hemodynamic stability, diagnosing neurologic death (should it occur), preparing the family for devastating news, counseling them on end-of-life issues, and preserving the option of organ donation. Once neurologic death is declared, the intensivist can still play an important role in maximizing the likelihood of successful organ procurement by collaborating with OPO personnel prior to family discussions about organ donation and by implementing appropriate management strategies to preserve organ function. Underscoring the integral role of the intensivist, a recent study from the University of Pittsburgh documented a significant increase in the number of transplantable organs recovered after implementation of an intensivist-led organ donor support team composed of a panel of on-call intensivists who assist the OPO with donor management (5).

As intensivists become increasingly involved in donor management, it is imperative that the same rigor that is applied to the care of living patients be employed in the care of organ donors. Standardized practices and guidelines regarding the critical care of potential organ donors are limited. A Canadian publication based on the 2004 forum, Medical Management to Optimize Donor Organ Potential, stands as one of the only attempts to develop expert consensus recommendations on ICU care of the potential donor across all organ types (6). Acknowledging the paucity of guidelines and the vital role played by the intensivist, the Society of Critical Care Medicine (SCCM) and the American College of Chest Physicians (ACCP) established a working group of experts in critical care medicine, organ transplantation, and donor management to create a consensus document on management of the potential organ donor in the ICU. The goal of this document is to provide critical care practitioners with essential information and practical recommendations to allow them to assume a central role in management of the potential organ donor. Through provision of meticulous and aggressive care, and in collaboration with the OPO and transplant teams, the intensivist has the opportunity to both preserve the option of organ donation for patients and their families and provide the gift of life to others.

METHODS

Members of the Donor Management Task Force are listed in **Appendix 1**. See the **online supplement I** (Supplemental Digital Content 1, http://links.lww.com/CCM/B250) for more extensive details of the process that was followed to assemble the task force, review the literature, and produce this document. Of note, it became clear from this process that the available literature overwhelmingly comprised observational studies and retrospective case series, representing low-quality evidence, with a notable scarcity of randomized controlled trials. For this reason, a decision was made by the co-chairs that the document would assume the form of a consensus statement rather than an evidence-based (and formally graded) guideline. As defined by the ACCP, a consensus statement is "a written document that represents the collective opinions of a convened expert panel. The opinions expressed in the consensus statement are derived by a systematic approach and traditional literature review where randomized trials do not commonly exist" (7).

Readers seeking a concise summary of the recommendations without the accompanying literature review are referred to **online supplement II** (Supplemental Digital Content 2, http://links.lww.com/CCM/B251).

DEATH DETERMINATION USING NEUROLOGIC CRITERIA

There are two sets of criteria for death determination. The first is the circulatory-respiratory criteria set, wherein the patient has permanently lost circulation, respiration, and responsiveness. The second is the neurologic criteria set, in which the patient has irreversible cessation of whole brain function including the brainstem. The neurologic criteria require permanently absent whole brain function clinically assessed by the absence of evidence of cortical function and brainstem reflexes and by apnea (8). When the neurologic criteria are satisfied, the patient is colloquially said to be "brain dead." In this section, we will use the terms "brain death criteria" and "neurologic criteria for death determination" interchangeably, although the latter term is technically more correct and preferred.

See online supplement I (Supplemental Digital Content 1, http://links.lww.com/CCM/B250) for additional background information on neurologic criteria for death determination.

In 1995, the Quality Standards Subcommittee of the American Academy of Neurology created medical standards for death determination using neurologic criteria that included methods of ancillary testing (cerebral angiography, electroencephalography, transcranial Doppler ultrasonography, and cerebral scintigraphy), as well as a checklist for the clinical examination and a requirement for ancillary testing when the clinical examination cannot be completed (8). In spite of these standards, variability exists in death determination standards among practice sites, especially in the requirements pertaining to minimal acceptable temperature, number of examinations, and observation period required between examinations (9). Although there is general agreement on the evaluation of brainstem reflexes, there are marked differences in the performance of the apnea test. In addition, the number of physicians required to diagnose brain death, as well as the type and need for confirmatory tests, varies among and within countries.

In 2010, the Quality Standards Subcommittee of the American Academy of Neurology published revised evidence-based recommendations for the determination of brain death among adult patients (9). The subcommittee noted that: 1) no evidence of recovery of brain function was observed among individuals who met the 1995 criteria, and therefore, they recommended that the guidelines be used; 2) complex motor activity can occur in patients who meet the criteria, so motion

does not exclude the diagnosis of death; 3) there is insufficient evidence to make a recommendation for a minimally acceptable observation period prior to diagnosing death using neurologic criteria; and 4) the apnea test is safe provided that apneic oxygenation methodology is used. This criteria set provides a checklist for brain death determination that may be useful to hospitals wishing to standardize practice and assure quality (**Table 1**).

Recommendation:

1. Organizations, hospitals, and governmental entities responsible for establishing and implementing neurologic criteria for the determination of death should incorporate the most recent recommendations provided by the Quality Standards Subcommittee of the American Academy of Neurology. The criteria should recognize that complex motor activity is possible among brain-dead individuals.

DONATION AFTER CIRCULATORY DETERMINATION OF DEATH

See online supplement I (Supplemental Digital Content 1, http://links.lww.com/CCM/B250) for background information on donation after circulatory determination of death (DCDD).

Are DCDD Outcomes Sufficient to Recommend This Source of Organs?

Kidney. DCDD has been used extensively for renal transplantation, and outcomes have been assessed. Some studies suggest that DCDD kidneys are associated with a significantly higher rate of delayed graft function compared with donation after neurologic determination of death (DNDD) kidneys (10–12), while other studies suggest a similar rate of this complication (13). When delayed graft function occurs, the long-term outcome appears to be similar or better in the DCDD recipients. Of those who developed delayed graft function in one study, graft survival in the DCDD recipients was better at 3 years (84%) compared with DNDD recipients (73%) ($p < 0.05$), as well as at 6 years (84% vs 62%, respectively) (11). Importantly, long-term graft survival of DCDD kidneys appears to be similar to that of DBDD kidneys (14–19). The prevalence of early graft failure is related to both warm and cold ischemic times (12). In an evaluation of 100 DCDD donors, warm ischemic time of 30 minutes or more was independently associated with early graft failure but not with 12-month graft survival (20). In a study of 2,562 DCDD kidney transplants, donor age and cold ischemic time were found to predict functional outcome. DCDD donors younger than 50 years old with cold ischemic times less than 12 hours had long-term graft survival similar to that of standard donors (21). Matsuno et al (10) found that for DCDD kidneys, a warm ischemic time of more than 20 min and a total ischemic time of more than 12 hours were associated with a significantly higher prevalence of primary graft nonfunction. Despite longer warm ischemic times, kidneys from donors whose life support was withdrawn in the ICU have similar outcomes compared with those organs from donors whose life support is withdrawn in the operating room (22). Successful renal transplantation has also been documented in uncontrolled DCDD patients receiving cardiopulmonary resuscitation, irrespective of its duration (23).

Although outcomes following DCDD kidney transplantation appear to be comparable to those following DNDD procedures, DCDD donation may be more costly due to the higher prevalence of delayed graft function, need for dialysis, longer initial hospital stays, and frequent readmissions (24). This must be balanced, however, with the impact DCDD has in terms of increasing the availability of organs for transplant which in turn decreases wait list mortality.

Liver. Several studies suggest that for properly selected donors, patient and graft outcomes following DCDD liver transplants are similar to those following DNDD (25–29). In a study of 874 adult DCDD liver transplants, Lee et al (30) found that the best graft survival occurred in young donors (≤ 47 yr) with warm ischemic time up to 15 minutes and cold ischemic time up to 10 hours. In another study involving the UNOS database, outcomes similar to DNDD were achieved when low-risk DCDD grafts were coupled with low-risk recipients; however, when all DCDD donors and recipients were considered, DCDD liver survival was inferior at 1 and 3 years (71% vs 80% and 60% vs 72%, respectively) (31). Other studies similarly suggest that outcomes following DCDD liver transplantation may have slightly inferior graft survival rates (32, 33). In an evaluation of 472 DCDD liver transplant recipients, the adjusted relative risk of graft failure was 1.85 compared to that of DNDD procedures (34). There appears to be an increased rate of biliary stricture, hepatic infections, and postoperative complications in recipients of DCDD livers (25, 32, 35, 36). DCDD liver recipients are more likely to develop postreperfusion hyperkalemia (37). The repeat transplantation rate is higher following DCDD due to a higher prevalence of nonanastomotic biliary strictures (26, 30, 38, 39). Only one small study of 19 DCDD recipients reported a rate of biliary complications similar to that of DNDD recipients (34).

Lung. Prior to 2008, published data on DCDD lung recipients were scarce and generally limited to case reports or series. Snell et al (40) reported on eight DCDD lung transplant patients with 100% survival at a mean of 311 days. However, a report on 17 out-of-hospital uncontrolled DCDD donors following cardiopulmonary resuscitation documented a 17% early and 31% 1-year mortality rate, leading to caution in the use of uncontrolled DCDD lungs (41). In 2008, a review of all controlled DCDD lung transplant cases ($n = 36$) in the U.S. OPTN database found a combined 2-year survival of 87% (42). More recently, two studies representing a combined total of 90 DCDD lung transplant procedures documented 1-year survival rates of 88–97% and 5-year rates of 82–90%; these compared favorably to survival rates achieved with use of conventional DNDD donors (43, 44). The recent introduction of ex vivo techniques to "condition" the lung allograft after recovery but prior to reimplantation in the recipient has the potential to further increase the use of DCDD lungs.

Pancreas. Data are limited on pancreas or simultaneous kidney-pancreas transplantations from DCDD donors. In one of the largest series, involving 31 simultaneous kidney-pancreas transplants from DCDD donors, there was no difference in

TABLE 1. Checklist for Determination of Brain Death

Prerequisites (all must be checked)

- ☐ Coma, irreversible, and cause known
- ☐ Neuroimaging explains coma
- ☐ CNS-depressant drug effect absent (if indicated, toxicology screen; if barbiturates given, serum level < 10 μg/mL)
- ☐ No evidence of residual paralytics (electrical stimulation if paralytics used)
- ☐ Absence of severe acid-base, electrolyte, and endocrine abnormality
- ☐ Normothermia or mild hypothermia (core temperature, > 36°C)
- ☐ Systolic blood pressure > 100 mm Hg
- ☐ No spontaneous respirations

Examination (all must be checked)

- ☐ Pupils nonreactive to bright light
- ☐ Corneal reflex absent
- ☐ Oculocephalic reflex absent (tested only if cervical spine integrity ensured)
- ☐ Oculovestibular reflex absent
- ☐ No facial movement to noxious stimuli at supraorbital nerve, temporomandibular joint
- ☐ Gag reflex absent
- ☐ Cough reflex absent to tracheal suctioning
- ☐ Absence of motor response to noxious stimuli in all four limbs (spinally mediated reflexes are permissible)

Apnea testing (all must be checked)

- ☐ Patient is hemodynamically stable
- ☐ Ventilator adjusted to provide normocarbia ($Paco_2$, 34–45 mm Hg)
- ☐ Patient preoxygenated with 100% Fio_2 for > 10 min to Pao_2 > 200 mm Hg
- ☐ Patient well-oxygenated with a positive end-expiratory pressure of 5 cm H_2O
- ☐ Provide oxygen via a suction catheter to the level of the carina at 6 L/min or attach T-piece with continuous positive airway pressure at 10 cm H_2O
- ☐ Disconnect ventilator
- ☐ Spontaneous respirations absent
- ☐ Arterial blood gas drawn at 8–10 min, patient reconnected to ventilator
- ☐ Pco_2 > 60 or 20 mm Hg rise from normal baseline value

OR

Apnea test aborted

Ancillary testing (only 1 test needs to be performed; to be ordered only if clinical examination cannot be fully performed due to patient factors or if apnea testing inconclusive or aborted)

- ☐ Cerebral angiogram (insufficient evidence to recommend use of CT or MRI angiography)
- ☐ Hexylmethylpropylene amineoxine single-photon emission CT
- ☐ Electroencephalography
- ☐ Transcranial Doppler ultrasonography

Time of death (MM/DD/YY) _____

Name of physician and signature _____

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5-year pancreatic and renal allograft survival compared with survival in transplants utilizing DNDD donors (45, 46).

Recommendation:

1. DCDD donation should be viewed by the critical care team as a potential pathway for organ donation, including liver, lung, kidney, pancreas, and in some instances heart donation. Such opportunities for donation should be pursued in conjunction with the local OPO and transplant centers.

What Is the Chance of Circulatory Death Within 60 Minutes After Withdrawal of Care?

Many institutions have developed standardized protocols for the DCDD process. The patient is generally transferred to the operating room, and circulatory function is monitored. After withdrawal of life support, the patient is observed until circulatory function ceases. Most protocols dictate that if circulatory cessation does not occur within 60 minutes, the patient is returned to the ICU and the procurement of organs aborted. Although the majority of cases go on to donation, predicting this is important from the perspective of the potential donor family, the awaiting recipient, transplant team, and other hospital resources. Utilizing the University of Wisconsin Donation after Cardiac Death Evaluation Tool to evaluate vital signs and respiratory parameters while the patient is disconnected from the ventilator for up to 10 minutes correctly predicts the likelihood of circulatory death at 60 minutes at a rate of 83.3% (47).

A UNOS DCDD Consensus Committee also developed criteria predictive of death within 60 minutes after withdrawal of life support (**Table 2**). DeVita et al (48) prospectively evaluated these criteria in 533 patients who had life support withdrawn and who were followed until death was declared. A total of 29%, 52%, 65%, and 82% of patients with 0, 1, 2, and 3 UNOS Consensus Committee DCDD criteria, respectively, died within 60 minutes of withdrawal of life support, leading the authors to suggest that patients with no criteria might be excluded from consideration (48). Whether to draw the threshold for attempted donation at least 1 or 2 criteria depends on the particular balance that a program wishes to achieve with respect to maximizing the number of DCDD donors identified versus minimizing manpower use, as well as emotional and resource costs associated with failed donations.

Using multivariable logistic regression analysis, a recent prospective multicenter study of 211 DCDD donors found that use of controlled mechanical ventilation was an independent risk factor for death within 60 minutes of withdrawal of life-sustaining therapy; controlled mechanical ventilation, norepinephrine administration, and absence of cardiovascular comorbidity were independent risk factors for death within 120 minutes. The clinical judgment of the intensivist predicted death within 60 and 120 minutes with a sensitivity of 73% and 89%, respectively, and a specificity of 56% and 25%, respectively (49).

Less is known about the likelihood of circulatory death within 60 minutes in pediatric DCDD donors. Of 254 deaths in a PICU, 24 were potentially eligible for controlled DCDD, 14 of whom died within 60 minutes of withdrawal for a yield of 5.5% of all PICU deaths (50). In another study of 12 pediatric DCDD patients, all went on to donation within 30 minutes of withdrawal (51).

TABLE 2. United Network for Organ Sharing Consensus Committee Criteria for Prediction of Death Within 60 Minutes of Withdrawal of Life-Sustaining Treatment

Apnea
Respiratory rate < 8 or > 30 breaths/min
Dopamine ≥ 15 μg/kg/min
Left or right ventricular assist device
Venoarterial or venovenous extracorporeal membrane oxygenation
Positive end-expiratory pressure ≥ 10 and $Sao_2 \leq 92\%$
$Fio_2 \geq 0.5$ and $Sao_2 \leq 92\%$
Norepinephrine or phenylephrine ≥ 0.2 μg/kg/min
Pacemaker unassisted heart rate < 30
IABP 1:1 or dobutamine or dopamine ≥ 10 μg/kg/min and CI ≤ 2.2 L/min/m^2
IABP 1:1 and CI ≤ 1.5 L/min/m^2

Sao_2 = arterial oxygen saturation, IABP = intra-aortic balloon pump, CI = cardiac index.

Recommendations:

1. Available scoring systems may be used in conjunction with expert clinical judgment to assist in identifying those potential adult DCDD donors most likely to undergo circulatory death within an established time that would permit successful recovery of organs. This time period may vary by transplant center.
2. In order to maximize the potential of adult DCDD donors, an increase in the number of unsuccessful cases must be acceptable.
3. Clinicians must be prepared for potential DCDD scenarios in which death does not occur within the established time after withdrawal of life-sustaining therapy. Appropriate protocols should be in place to return the patient to a critical care setting for continuing care and to provide appropriate family support.

What Is the Role of Extracorporeal Membrane Oxygenation in DCDD?

Warm ischemic time prior to the instillation of cold perfusate appears to have a significant role in subsequent organ function. The time from significant hypotension to cold perfusion is more important than the time from extubation and withdrawal of care to cold perfusion (52). For this reason, extracorporeal membrane oxygenation (ECMO) has been advocated to preserve organs for transplant. In 2000, Ko et al (53) reported the Taiwanese experience with four patients who received ECMO following circulatory death, with the successful retrieval of

eight kidneys. In 2004 and 2005, investigators from the University of Michigan reported two series of patients whose organs were preserved with ECMO upon declaration of cardiac death (54, 55). The technique used by these researchers was to carefully select patients who had devastating brain injury but did not meet brain death criteria. If the patient was deemed suitable for organ donation, the family was approached for authorization. Following authorization, ECMO cannulas were inserted into the femoral artery and vein and support was withdrawn. If circulatory death occurred within 60 minutes, an aortic occlusion balloon was inflated and the distal aorta perfused without restoring cardiac or cerebral circulation. Abdominal organs were then retrieved while being perfused by the circuit. One report utilized ECMO without specifying the use of aortic occlusion and suggested the potential to retrieve thoracic organs. However, the application of ECMO in DCDD patients is controversial, and some have questioned the ethics of thoracic aortic occlusion in an attempt to prevent the reestablishment of cerebral circulation (56). Several investigators have explored the use of ECMO in uncontrolled DCDD applications to increase the pool of kidneys and livers (57, 58). Despite the theoretical benefits, no large clinical trials have compared organ retrieval outcomes with and without ECMO. Furthermore, if ECMO with oxygenation restores circulation to the brain, it negates the prior death determination.

Recommendation:

1. Although a physiological basis for using an ECMO circuit to preserve abdominal organ function in DCDD is sound and preliminary data are encouraging, further study is warranted before widespread implementation.

AUTHORIZATION PROCESS

Are Any Family Characteristics Associated With the Probability of Authorizing Organ Donation?

Two characteristics have been associated with lower rates of authorization (previously referred to as "consent") for organ donation. First, families who express uncertain understanding of the potential donors' wishes are less likely to authorize donation (59). Second, African American families have consistently been found to be less willing to donate than Caucasian families (60–64). These racial differences, likely rooted in historical distrust in the healthcare system (65), are compounded by observations that caregivers and OPO representatives may have less detailed conversations when discussing organ donation with African American families (63).

Recommendations:

1. Regardless of family demographics or other characteristics, ICU caregivers and OPO representatives should provide all patients with equal opportunities for organ donation.
2. Clinicians and OPO representatives should be aware that a patient's own authorization for organ donation through a donor registry is increasingly common and that this can assist in conveying the potential donor's wishes to the family.

Does the Timing of the Request for Deceased Organ Donation Influence the Probability of Authorization?

Timely notification of the OPO is essential. It is defined by CMS regulation as notification of an impending death within 1 hour of one or more specified clinical triggers (**Table 3**) being met. Timely notification increases the period available to evaluate a patient's medical suitability for donation and to relay information about the opportunity to families in a manner that minimizes time pressures as much as possible. This may improve the quality of the authorization process and increase the proportion of eligible donors who go on to donate (66). Early OPO notification does not preclude intensivists from discussing end-of-life decisions with families, although the specific discussion about organ donation should include the OPO staff. The rapid notification allows the OPO to begin the process of assessing donation potential and to develop a collaborative plan for approaching the family after intensivists have discussed end-of-life care. Additionally, although early notification may help actualize a patient's previously stated preferences for organ donation or registered donor status, donation preferences need to be coordinated with other end-of-life preferences, such as the timely withdrawal of life-sustaining therapies (67).

Several experts have recommended separating requests for donation from the family notification of brain death, a process known as "decoupling" (68, 69), but one analysis suggested that decoupling does not significantly improve authorization rates after neurologic determination of death (70). The influence of decoupling on family grieving and perceptions of the quality of end-of-life care has not been examined. There are ethical reasons to separate the decision to withdraw life-sustaining therapies from the decision to pursue organ donation. In the case of DCDD, such separation may be essential to quell real or perceived conflicts of interest among ICU caregivers (71, 72). On occasion, patients or families may raise the issue of donation prior to death determination or discussion of withdrawal of life-sustaining therapy or be aware of the patient's status as a registered donor. In those situations, the clinician should be careful to ensure that the decision to withdraw life-sustaining treatments is separate from the decision to donate.

Recommendations:

1. ICU caregivers should notify OPOs within 1 hour after a patient meets specified clinical triggers (Table 3).
2. Clinicians should consider organ donation as part of end-of-life decisions.

TABLE 3. Examples of Clinical Triggers That Should Prompt Notification of the Organ Procurement Organization

At the initial indication that a patient has suffered a nonrecoverable neurologic injury (e.g., documented loss of cranial nerve reflexes)
As soon as a formal "brain death" examination is contemplated
Before initiating a discussion that may lead to withdrawal of life-sustaining therapy

3. The effects of the timing of an organ donation request relative to disclosure of brain death on family bereavement should be further studied. Pending additional data, informing the family of the patient's death, should be separated from requests for organ donation.

Who Should Request Authorization?

Since 1998, Conditions of Participation of the Centers for Medicare and Medicaid Services have required hospitals to use "designated requestors" to obtain family authorization for donation (69). This policy stems, in part, from studies documenting higher conversion rates when authorization is requested by personnel with substantial experience and interest in helping families understand and cope with the organ donation process (59, 73). Although most of these individuals are OPO representatives, some physicians, nurses, social workers, and pastoral care workers have developed the necessary skills to serve effectively as designated requestors.

Given the known increases in authorization rates when trained personnel make requests, in-house OPO coordinators have been strategically placed in some level I trauma centers to handle all authorization issues. Although randomized trials of in-house coordinators are lacking, observational reports from these centers have consistently shown increased conversion rates following the introduction of an in-house OPO coordinator (74–77). Also, it is unknown whether similar increases in conversion rates could be obtained by training nurses, social workers, or other hospital employees. Finally, it remains uncertain whether the increased conversion rates associated with in-house coordinators are related to superior communication skills, increased time with families of potential donors, contemporaneous changes in hospital culture, increased familiarity and improved working relationship between hospital and OPO staff, or some combination of these factors.

Evidence also suggests that coordination of efforts between the requestor and the primary clinical team is associated with increased conversion rates. In a study of 420 deceased potential organ donors from 1994 to 1999, Siminoff et al (59) found an optimal sequence for successful requests: initial approach by a nonphysician member of the primary healthcare team, followed by detailed discussion with an experienced OPO coordinator.

More research is needed to determine whether authorization rates can be improved by 1) "like requestors" (requestors of racial or religious backgrounds similar to those of the potential donors); 2) direct refutation of false beliefs; and 3) a second approach after initial refusal.

Recommendations:

1. OPO representatives or designated requestors who have met the regulatory requirements and have sufficient experience and time should request authorization for organ donation in all institutions, using a collaborative approach with the rest of the healthcare team.
2. Coordination of the goals of the healthcare team and OPO representatives should be a priority for all ICUs.
3. In-house organ donation coordinators should be considered in institutions with a high volume of potential donors (e.g., level I trauma centers).

What Is the Role of First-Person Authorization When It Is Available?

In an increasing number of cases, patients will have expressed desires to become organ donors before becoming moribund. This first-person authorization can take several forms: inclusion in a donor registry, notation on the driver's license, presence of a donor card, documentation of preferences with their primary care provider or a durable power of attorney; or explicit preferences in an advance directive.

Legally, first-person authorization provides sufficient grounds for organ procurement in all 50 states and Washington, DC (78). Under the Uniform Anatomical Gift Act, surrogates are prohibited from overriding an individual's previously expressed authorization. Significant provisions related to first-person authorization are included in the 2006 revision to the Uniform Anatomical Gift Act, which has been adopted in 42 states and Washington, DC, at the time of this writing (79).

Currently, with over 100 million adults in the United States registered as donors, a significant percentage of potential organ donors have made their own donation decision. In 2012, 40% of actual organ donors in the United States authorized donation through a donor registry (80). The impact of donor registration on DCDD has yet to be studied but will likely play an increasingly important role in the future.

Given the legal authority of first-person authorization and the growing number of registered donors, ICU clinicians and OPOs are sensitive to the fact that, on occasion, they may have to manage conflicts between the patients and their surrogates. Conflicts are typically addressed on a case-by-case basis and involve collaboration between the OPO staff, hospital clinicians, OPO leadership, hospital administration, and the patient's family. A recent survey of OPO directors suggested that a strong majority would recover organs from a DBDD candidate who had provided first-person authorization if surrogates had objections (81). The majority of OPOs indicated that educating families about the donor designation and achieving familial agreement with the wishes of the deceased were a key part of this process. First-person authorization has been reported for patients with cognitive function on life-sustaining therapy; in this situation, this is reasonable as long as the rationale for having life-sustaining treatments withdrawn is not organ donation (82, 83).

Recommendation:

1. A patient's previously expressed preferences for organ donation are paramount. ICU clinicians and OPOs should inform the decedent's family of the legality of first-person authorization.

GENERAL CONTRAINDICATIONS TO ORGAN DONATION: MALIGNANCY AND INFECTION

Is Malignancy a Contraindication to Organ Donation?

Malignancy Not Involving CNS. Information on transmission of malignancies not involving the CNS is derived largely from the Israel Penn International Transplant Tumor Registry (IPITTR) (84), which has tracked the outcomes of

transplantation involving donors with known or incidentally discovered malignancies for over four decades. The high rates of documented transmission likely reflect an overestimation of the true risk, as the registry is built upon voluntary reporting of index cases of transmission and may fail to appreciate the entire at-risk population of recipients who did not develop malignancy. Since 1996, UNOS has also maintained data on outcomes of transplantation utilizing donors with active or past history of malignancy, but the completeness of the database in tracking development of cancer has been called into question. For example, one study demonstrated that the UNOS database captured only half of the cancer cases recorded in a comprehensive Surveillance, Epidemiology, and End Results Program established within a single UNOS region (85). Thus, the true risk of donor transmission likely lies between the estimates offered by these two sources.

The IPITTR identified several tumors with exceedingly high rates of transmission (i.e., percentage of recipients who developed malignancy after receiving organs from affected donors) (83). Choriocarcinoma, a highly aggressive gynecological malignancy, had a transmission rate of 93%. Malignant melanoma had a transmission rate of 74%. Utilization of organs from donors with an active or past history of lung cancer resulted in a transmission rate of 43%. Renal cell carcinoma had a transmission rate of 63%, almost exclusively confined to the renal allograft itself, but no transmission to recipients occurred among 14 cases of low-grade renal cell carcinomas that were free of extracapsular or vascular invasion and excised ex vivo before implantation.

The IPITTR contains far less information on other common malignancies. A transmission rate of 19% was reported in association with the use of donors with a history of colon cancer, but details on the stage and disease-free periods are lacking. Based on an exceedingly low risk of nodal or metastatic disease associated with T1 primary tumors in the general population, a 2003 consensus conference of the American Society of Transplant Surgeons endorsed the use of donors with T1 colon cancers and a minimum of 1-year disease-free interval for white male donors and 5 years for female donors independent of race (86). Because early-stage colon cancer behaves in a more aggressive fashion in African-American men, it was recommended that organs from this population not be used no matter the disease-free interval.

The IPITTR offers scant data on donors with a history of breast cancer. Although an overall transmission rate of 29% was documented, no transmission occurred in cases involving in situ cancers (ductal carcinoma in situ and lobular carcinoma in situ), and use of such donors was endorsed (84).

In contrast to the IPITTR, the UNOS database documents a low risk of donor transmission. The latest report, published in 2007, identified 1,090 transplants involving donors with a history of malignancy other than CNS tumors and nonmelanoma skin cancers (87). Among 140 transplants involving donors with a history of melanoma, only one case of donor transmission was identified; notably, the donor had a 32-year disease-free interval before organ donation. Despite the seemingly low rate of transmission, the UNOS authors concluded that "a history of melanoma is an absolute contraindication for a patient to be eligible for organ donation." (87) No cases of transmission were noted with any other tumor type, including breast (n = 126 transplants), lung (n = 10), ovarian (n = 75), and colorectal carcinoma (n = 38). However, no information related to tumor stage was provided, and most cases involved donors with cancer-free intervals exceeding 10 years.

Limited but favorable information is available on the transmission potential of localized prostate cancer. Five cases detected in donors have been reported to UNOS. In each case, small moderately differentiated adenocarcinomas restricted to the prostate gland were incidentally found at donor autopsy; no reports of transmission to organ recipients have been documented (88). An autopsy series of "healthy" organ donors found that 23% of donors aged 50–59 years and 35% of those aged 60–69 years, respectively, had unsuspected prostate cancer (89). Despite this high prevalence and the increased use of older donors, no cases of transmission of prostate cancer have been reported to UNOS since the advent of mandatory reporting of donor-derived diseases in 2005 (88). These findings suggest that the transmissibility of localized, early-stage prostate cancer is likely remote.

Recommendation:

1. Although donor transmission of malignancy has been documented, there are no absolute contraindications. The risks of donor transmission must be weighed against the risk to the potential recipient of not receiving the organ. Determinations about an individual donor's medical suitability for organ donation should be made in conjunction with the local OPO and the involved transplant centers.

CNS Malignancies. CNS tumors represent the second most common malignancy (behind skin cancer) encountered in donors with a history of cancer (90). In most cases, the malignancy is active or recent, rather than remote, and is often the cause of death. Because extraneural spread of primary CNS malignancies is rare (reported rates between 0.4% and 2.3%), organs have commonly been recovered from affected donors.

Two single-center retrospective case series, involving a total of 132 recipients of organs from 47 donors with CNS tumors, documented a transmission rate of 2.2–3% (91, 92). Three large transplant registries have also provided data, albeit conflicting. The largest of these is the OPTN/UNOS registry, which identified 642 recipients of organs from donors with CNS tumors between the years 2000 and 2005. Only three cases of disease transmission were recorded, all arising from a single donor with glioblastoma multiforme (87). The transmission rate was 0.5% when all recipients were considered and 1.7% when the analysis was restricted to recipients from donors with glioblastoma multiforme. Similarly, the Australia and New Zealand Registry identified 153 recipients of organs from 46 donors with CNS tumors. No cases of transmission were reported at a mean follow-up of 40 months (93).

In contrast, the IPITTR suggests a much greater risk of tumor transmission. Again, this discrepancy may reflect the nature of the database, which encourages reporting cases of tumor

transmission and may grossly underestimate the number of unaffected recipients. In the 2004 report, 36 donors with CNS tumors were identified, resulting in donation to 62 recipients. The overall transmission rate was 23%. Risk factors for tumor transmission were high-grade malignancy (grades III–IV), previous craniotomy, and presence of a ventriculoperitoneal or ventriculoatrial shunt. The risk of tumor transmission was 7% in the absence of any risk factor and 46% when at least one risk factor was present (84). Also included in the IPITTR database were 29 donors with metastases to the brain misdiagnosed as intracerebral hemorrhages or primary CNS malignancies (94). Among 42 recipients of organs from the donors with unrecognized brain metastases, tumor transmission rate was 74%.

Recommendations:

1. Individuals with CNS tumors of low histological grade (grades I–II) and no history of craniotomy, brain irradiation, or ventricular shunts carry a low risk of tumor transmission and should be considered suitable organ donors.
2. The medical suitability for organ donation of donors with high-grade (grades III–IV) CNS malignancies and/or who have undergone craniotomy or placement of a ventriculoatrial or ventriculoperitoneal shunt should be made in conjunction with the local OPO and the involved transplant centers. The risks of donor transmission must be weighed against the risk to the potential recipient of not receiving the organ.
3. Potential donors with uncertain etiologies for brain death, particularly otherwise unexplained intracerebral hemorrhage or suspected primary CNS tumors without histological confirmation, should be considered for limited brain autopsy immediately after donation, if resources are available to do so.

Is Donor Bacteremia and/or Sepsis a Contraindication to Organ Donation?

Critically ill patients admitted to the ICU may require the introduction of intravascular catheters and other indwelling monitoring devices for optimal care. For those being considered for donation, the risk of infection and subsequent organ contamination must be considered before procurement. If these potential donors were not infected at admission, evidence of any infection resulting from catheter or device placement must be sought.

The finding of positive blood cultures in prospective organ donors is not unusual and has exceeded 20% in some series. Despite this, the actual transmission rate to recipients may be considerably less (95); however, should transmission occur, it may adversely affect 1-year posttransplant mortality (96). Blood culture positivity appears to be more common in older donors and those who are in the ICU for at least 3 days. Donors in the ICU for more than 48 hours have an increased risk of bacteremia, resulting from coagulase-negative staphylococci, likely secondary to intravascular devices. Infection in young donors (< 40 yr) is closely correlated with bacteremia due to Gram-positive organisms (i.e., *Staphylococcus aureus*), whereas older donors (> 50 yr) have a greater risk of Gram-negative bacteremia (97). Organs from bacteremic donors have been successfully procured, resulting in few, if any, transmitted infections when the donor received pathogen-specific antibiotics for a minimum of 48 hours before procurement (98).

In those cases where recipients received organs from donors whose blood culture positivity was not discovered until after procurement, neither mortality nor graft dysfunction appeared to be greater compared to recipients of noncontaminated organs, provided the recipients were treated with 7–14 days of antibiotics specific to the recovered pathogen (99, 100). Furthermore, although most series reported equivalent graft and survival outcomes with utilization of pathogen-specific antibiotics, one series found good outcomes utilizing only a standard posttransplant antibiotic regimen (101).

The risks associated with organs from donors with fungemia have not been reported.

Recommendations:

1. Bacteremia or bacterial sepsis should not be considered an absolute contraindication to organ donation.
2. If bacteremia is identified in a donor, pathogen-specific antibiotics should be administered as soon as possible. Delaying organ procurement until the donor has received antibiotic therapy for at least 48 hours should be considered.

Can Patients With Meningitis Donate Organs?

Several single-center case series have examined the use of organs from donors with documented or presumed bacterial meningitis (102–105). The most common pathogens were *Neisseria meningitidis*, pneumococcus, and *Haemophilus influenzae*. All donors received appropriate antibiotics for variable periods before organ procurement, and these antibiotic regimens were continued in the recipients. No cases of donor transmission of infection were reported. No evidence of compromised survival was found in those studies that compared outcomes with a noninfected control group. Bacterial meningitis caused by *Listeria monocytogenes* generally requires a longer course of therapy and has a higher risk of relapse.

Transmission of lymphocytic choriomeningitis virus (106) and rabies virus (107) from donors to solid-organ transplant recipients has been reported. Due to the nonspecific nature of donor signs and symptoms, the apparent presence of alternative diagnoses for the donors' CNS impairment, and the unusual nature of the pathogens involved, these infections were not suspected or identified before organ procurement. Only when multiple recipients fell ill did extensive investigation reveal the cause and origin.

Recommendations:

1. Patients with bacterial meningitis are suitable organ donors as long as they have received therapy directed against the known or presumed pathogen. There is no consensus on the duration of donor treatment before organ procurement, but a course of 24–48 hours has been suggested by several authors. The organ recipient should be treated with a similar antibiotic regimen for 5–10 days.
2. Organs should not be procured from patients with undiagnosed febrile illnesses, encephalitis, meningitis, or flaccid paralysis of unknown etiology.

Should Seronegative Patients With High-Risk Behaviors Associated With HIV Infection be Used as Organ Donors?

Use of organs from donors who test positive for HIV is absolutely contraindicated for non–HIV-positive recipients because of the risk of viral transmission. In November 2013, the HIV Organ Policy Equity Act was signed into law in the United States, supporting research efforts to determine the potential benefits of transplanting organs from HIV-positive donors into HIV-positive recipients, but this practice is not currently in effect.

Even among seronegative donors, there have been rare instances of HIV transmission; some but not all of these donors had known risk factors for HIV (108, 109). This phenomenon is largely attributable to the viremic window that follows acute acquisition of infection but precedes development of antibodies detectable by available enzyme-linked immunoassay testing methods. False-negative testing can also result from hemodilution after the donor has received a large volume of transfused blood products. To minimize the risk of false-negative HIV antibody test results caused by hemodilution, any blood sample obtained for HIV antibody testing is required to be assessed for hemodilution in accordance with OPTN policy to determine if it is a qualified specimen.

Organs from patients with a positive screening test for HIV antibodies are not suitable for transplantation unless subsequent confirmation testing indicates that the original test results were falsely positive. If multiple tests related to HIV are performed, the results of all tests must be communicated directly to all institutions receiving organs from the donor.

The Public Health Service has developed behavioral criteria that define donors at increased risk of having acquired HIV infection (as well as hepatitis B and C) (**Table 4**) (110). The estimated risk of undetected viremia among seronegative donors with these behaviors varies with the behavior category (111). The estimated risk per 10,000 donors is 12.1 for IV drug users, 10.2 for men who have had sex with other men, 6.6 for commercial sex workers, 2.3 for inmates of correctional facilities, 1.5 for persons exposed to HIV-infected blood in the past 12 months, 0.7 for persons who have had sex with a high-risk individual in the past 12 months, and 0.09 for hemophiliacs.

The use of nucleic-acid amplification testing (NAT) to detect the presence of HIV RNA reduces the likelihood of unrecognized viremia by approximately half in all high-risk behavior categories (111). A 2011 survey of OPO practices in the United States documented that 68% of OPOs routinely performed NAT testing on all potential donors, and another 30% performed such testing selectively on those with high-risk behavior characteristics (112). A multisociety consensus report recommended against NAT in screening donors with no identifiable high-risk behaviors, arguing that the false-positive rate in this group outweighs the likelihood of identifying true-positive infections. Use of NAT was recommended for high-risk behavior groups to reduce the risk of HIV transmission and to potentially increase organ utilization from the NAT-negative donors (112).

TABLE 4. Public Health Service Criteria for Donors at Increased Risk for HIV, Hepatitis B, and Hepatitis C Infections (141)

People who have had sex with a person known or suspected to have HIV, HBV, or HCV infection in the preceding 12 mo
MSM in the preceding 12 mo
Women who have had sex with a man with a history of MSM behavior in the preceding 12 mo
People who have had sex in exchange for money or drugs in the preceding 12 mo
People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 mo
People who have had sex with a person who injected drugs by IV, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 mo
A child who is 18 mo old and born to a mother known to be infected with, or at increased risk for, HIV, HBV, or HCV infection
A child who has been breastfed within the preceding 12 mo, and the mother is known to be infected with, or at increased risk for, HIV infection
People who have injected drugs by IV, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 mo
People who have been in lockup, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the preceding 12 mo
People who have been newly diagnosed with, or have been treated for, syphilis, gonorrhea, *Chlamydia*, or genital ulcers in the preceding 12 mo

HCV = hepatitis C virus, HBV = hepatitis B virus, MSM = men who have had sex with men.

Potential donors in high-risk behavior groups who test negative by enzyme-linked immunosorbent assay, with or without NAT, should not be excluded from consideration; the small risk of occult HIV transmission must be weighed against the urgency for transplantation. UNOS and the Center for Medicare and Medicaid Services mandate that information related to high-risk donor behavior be shared with the transplant teams; in turn, members of the transplant teams must inform the potential recipient who, after weighing the potential risks and benefits, is afforded the final decision in accepting the organ.

Recommendations:

1. Patients who are seronegative for HIV, but who meet any of the high-risk behavioral criteria for HIV infection, should not be excluded from organ donation. Use of organs in such circumstances is appropriate when the risk of not performing the transplant is deemed to be greater than the risk of HIV transmission. The OPO, transplant teams, and potential recipients must be notified of the presence of high-risk behavior in the donor history, and the potential recipients have the ultimate right to decline.
2. The use of NAT should be considered when evaluating seronegative donors with high-risk behavioral characteristics.

Is Donor Hepatitis C or B Seropositivity a Contraindication to Organ Donation?

Organs from donors who are seropositive for hepatitis C virus (HCV) may be considered suitable for use in HCV-positive recipients. This practice is most commonly employed in liver transplantation and, to a lesser extent, kidney transplantation (113, 114). The presence of hepatitis B virus (HBV) surface antigen remains an absolute contraindication to organ donation, although some centers will accept organs from donors testing positive for HBV core antibody under special circumstances. This practice carries a small risk of viral transmission for liver transplant recipients, and use of HBV immunoglobulin or oral antiviral therapy has been advocated to minimize this risk (115). The use of HBV core antibody-positive donors for lung transplantation appears to carry an extremely low risk of viral transmission (116, 117).

Recommendations:

1. Donor HCV seropositivity is not an absolute contraindication to organ donation; these organs may be directed for use in HCV-positive recipients.
2. Patients who are positive for HBV surface antigen are generally not considered for organ donation. In contrast, organs may be procured from patients who are positive for HBV core antibody.
3. Given the complexity of these issues, ICU staff should discuss issues of donor suitability related to HBV and HCV status with the OPO representative and transplant teams.

HEMODYNAMIC MANAGEMENT

See online supplement I (Supplemental Digital Content 1, http://links.lww.com/CCM/B250) for a detailed description of hemodynamic alterations associated with brain death.

What Are the Appropriate Goals of Fluid Management for Organ Preservation in the Donor Patient?

The primary goal of fluid management is to maximize perfusion for organ preservation, which can be achieved by ensuring adequate intravascular volume and appropriate cardiac output (CO). IV fluid therapy and hemodynamic management require monitoring tools. A central venous catheter and/or pulmonary artery catheter provide continuous measurements of volume-specific hemodynamic parameters, such as central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), CO, and cardiac index. Other semi-invasive devices that employ calibrated or noncalibrated pulse contour analysis to calculate CO, stroke volume, and stroke volume variation may be valuable but have not been well studied in the donor population.

A frequent challenge of volume therapy is the potential for antagonistic goals for kidneys and lungs. Traditionally, aggressive fluid resuscitation and management were thought to result in improved procurement of kidneys, while a conservative fluid replacement strategy benefited lung procurement. In a study by Miñambres et al (118), 404 kidney recipients demonstrated that a negative or equalized fluid balance with CVP less than 6 mm Hg affected neither renal graft survival nor development of delayed graft function. An analysis by Abdelnour and Rieke (119) evaluated the combination of hormone replacement therapy (HRT) and CVP-targeted approach on organ procurement, finding that standardized HRT plus a CVP less than 10 mm Hg significantly improved heart and lung procurement along with an increased availability of kidneys for transplantation (119). Despite this support, most management guidelines suggest that renal viability may be at risk in the absence of liberal hydration. When the lungs are not being considered for transplantation, a more aggressive fluid resuscitation may be warranted and necessitates optimal mechanical ventilatory management for systemic oxygenation.

Most hemodynamic goals are derived from case series, empiric protocols, or consensus conferences. The Crystal City consensus meeting for donor management guidelines recommended hemodynamic targets largely based on expert opinion and the successful organ yield improvement program at Papworth Hospital in Great Britain (120, 121). Specific variables of adequate volume resuscitation include mean arterial pressure of 60–70 mm Hg, urinary output 1–3 mL/kg/hr, decrease in dose of vasoactive agents (dopamine ≤ 10 μg/kg/min), and left ventricular ejection fraction of at least 45% (122, 123). Serial CVP and PAOP measurements should guide volume-targeted therapy, although impaired left ventricle compliance and distortions in the pressure-volume relationship related to brain death may affect accurate interpretation.

Recommendations:

1. Hypovolemia frequently is present at brain death and must be addressed promptly.
2. Hemodynamic monitoring tools aid in assessment of volume status and response to therapy. Pulmonary artery or central venous catheter insertion or noninvasive monitoring techniques should be considered, and serial or continuous measurements of CVP, PAOP, stroke volume, CO, cardiac index, and mixed venous oxygen saturation should be monitored.
3. General guidelines for adequate IV fluid resuscitation are as follows:
   a. Mean arterial pressure at least 60 mm Hg.
   b. Urine output at least 1 mL/kg/hr.
   c. Left ventricle ejection fraction at least 45%.
   d. Lower vasopressor dose (e.g., dopamine ≤ 10 μg/kg/min).
4. Fluid replacement using hemodynamic parameters, particularly CVP or PAOP, and targeted at maintaining euvolemia of the donor, is recommended during the entire donor management phase of care.

Is There a Preferred Resuscitation Fluid for Organ Preservation?

As the initial goal of fluid therapy in donors is intravascular volume replacement, an isotonic crystalloid is the preferred choice. Traditionally lactated Ringer solution or 0.9% saline has been used, but studies specifically addressing the choice of solution in this population are lacking. Coexisting

hyperchloremic metabolic acidosis may preclude the use of 0.9% saline. Similarly, the hypoosmolar effects and electrolyte content of lactated Ringer solution may not be advisable for some donors. In these situations, pH-neutral isoosmolar solutions may be considered. If volume status is stabilized but correction of hypernatremia is needed, hypotonic fluids (e.g., D5W) can be used. Patients with metabolic acidosis may benefit from solutions containing sodium bicarbonate; depending on the phase of volume replacement and the degree of hypernatremia, 50–150 mmol/L may be used. In hypernatremic donors, 0.45% saline with or without sodium bicarbonate can be used.

Colloidal solutions are used mostly as bolus infusions for acute intravascular volume expansion to resolve rapidly developing hypotension. Albumin 5% and hydroxyethyl starch (HES) are commonly available in ICUs. HES use is associated with acute kidney injury, coagulopathy, and trapping in the hepatic reticuloendothelial system; it can also cause acute hypervolemia with an adverse impact on potentially compromised right ventricular performance. Delayed graft function and graft failure have been associated with use of HES in donor management (124). Rapidly degradable low-molecular-weight HES solutions may have a better side-effect profile, as suggested by a study in which 130-kDa HES was compared with 200-kDa HES and demonstrated a trend toward decreased delayed graft function (125). The routine use of HES cannot be recommended based on available data, but if it is used, the infused volume should be limited to 500–1,000 mL.

Packed RBCs may be required to address severe anemia that could potentially compromise oxygen delivery to vital organs. The optimal hemoglobin in this population is unknown, but in other critically ill populations, a target above 7 g/dL has been recommended (126). Other blood products (fresh-frozen plasma, cryoprecipitate, and platelets) may be required to manage associated hematologic problems or bleeding. All of these blood products can also serve as colloidal volume replacement.

Recommendations:

1. Initial intravascular volume replacement with crystalloids or colloids is acceptable.
2. The recommended isotonic crystalloids are 0.9% saline and lactated Ringer solution.
3. HES should not be used routinely for colloidal resuscitation in organ donors.

Are There Preferred Vasoactive Drugs Used for Organ Preservation in the Donor?

Vasoactive support in the brain-dead donor includes administration of agents to support the cardiovascular system consequent to the effects of brainstem death pathophysiology. Hence, the discussion of these medications is not limited to the use of vasopressors and inotropes alone but includes HRT (vasopressin, steroids, and thyroid hormone).

Deleterious cardiac effects of the autonomic storm, including catecholamine-induced tachycardia and increased myocardial oxygen consumption, can be mitigated by using adrenergic antagonists such as esmolol (127). Some have advocated treating this phase to enhance heart procurement rates. The autonomic surge is the donor's compensatory response to increased ICP with incipient herniation; brain death has not yet manifested. In this circumstance, targeted therapy directed at the elevated ICP is appropriate as potential donor management should not be initiated until brain death is declared.

Once circulatory shock is established, the use of vasopressor agents is recommended when correction of the volume deficit fails to achieve the threshold hemodynamic goals. Vasoactive support should escalate to meet the defined hemodynamic goals, especially when initial echocardiography shows evidence of left ventricular dysfunction. The presence of stress cardiomyopathy should prompt the use of invasive and noninvasive hemodynamic monitoring.

Dopamine has traditionally been the first-line vasoactive agent in this population due to its inotropic and vasopressor effects. Norepinephrine and phenylephrine infusions should be used sparingly due to concern about their more potent α-receptor agonist activity compared with dopamine. α-Receptor stimulation predisposes to increased pulmonary capillary permeability, leading to increased extravascular lung water, and may also lead to coronary and mesenteric vasoconstriction. Catecholamines, especially dopamine, have immunomodulatory properties that may attenuate the effects of upregulation of the proinflammatory cytokine cascade. Dopamine protects against ischemia/reperfusion injury and inflammation by induction of enzymes like heme oxygenase-1 (128). Preprocurement treatment with dopamine is associated with faster alveolar fluid clearance and a reduced need for dialysis after kidney transplantation (129). Schnuelle et al (130) studied the effects of low-dose dopamine (4 μg/kg/min) on 264 brain-dead donors, resulting in 487 kidney transplants; the need for dialysis was significantly reduced in the dopamine-treated graft (24.7% vs 35.4%, $p = 0.01$).

Vasopressin improves the vasodilatory shock state associated with brain death (131), effectively counteracts diabetes insipidus (DI), and reduces the need for catecholamines. Effects mediated via stimulation of vascular V1a receptors, nitric oxide signaling pathways, and potassium channels in vascular smooth muscle cells account for systemic vasoconstriction (132). Due to these properties, vasopressin infusion is increasingly used as a first- or second-line agent in hemodynamic management of brain death. In one randomized controlled trial evaluating the use of HRT, the initiation of vasopressin led to a complete withdrawal of norepinephrine, which resulted in an improvement in cardiac performance (133). Use of vasopressin in deceased organ donors has been associated with an increased rate of organ recovery (134).

Norepinephrine is similarly used as an additional or secondary agent in the potential donor, mostly when dopamine infusion rates approach more than 10 μg/kg/min or marked hemodynamic instability is present. The use of norepinephrine in donors has been associated with a reduced 1-year survival in heart transplant recipients (132).

HRT utilizes combinations of thyroid hormone and corticosteroids. It is frequently given upon the initiation of donor

management independent of hemodynamics or reserved for unstable donors unresponsive to fluids and/or vasoactive support. The use of HRT for hemodynamic support will be discussed in the next section.

Recommendations:

1. Dopamine has traditionally been the first-line vasoactive agent for management of cardiovascular collapse following brainstem death, but there remain insufficient data to preferentially recommend this over other vasopressor agents.
2. Vasopressin infusion is an alternative first-line agent and can also serve as an additional vasopressor in cases of refractory shock.
3. Norepinephrine, phenylephrine, and other vasoactive agents (e.g., dobutamine and epinephrine) may be used in severe shock.
   a. Dopamine, dobutamine, or epinephrine may be used in primary cardiac pump dysfunction.
   b. Norepinephrine or phenylephrine is recommended in the predominantly vasodilatory component of shock (low systemic vascular resistance).
4. If hemodynamic goals are not met and/or left ventricular ejection fraction remains less than 45%, HRT may be undertaken.

What Is the Preferred Approach to Hemodynamic Monitoring in the Brain-Dead Donor?

Markers of global tissue hypoxia and impaired oxygen extraction, such as mixed venous oxygen saturation, lactic acid levels, base deficit, cardiac flow, and filling pressures, provide an assessment of shock-associated injury related to numerous shock states in critically ill patients. Unfortunately, there have been no major studies to establish baseline metrics to assess the utility of these variables in the DBDD physiological state, and data interpretation must be extrapolated from other shock state-related variables. Placement of CVP or pulmonary artery catheter or use of noninvasive hemodynamic monitoring is recommended to assess right and left heart filling pressures, CO, stroke volume, and fluid responsiveness. Echocardiography is needed to assess the state of the myocardium and to evaluate for other related cardiac pathology, such as valvular or pericardial disease, prior to acceptance for transplantation. Initial transthoracic echocardiography (TTE) findings of impaired left or right heart function may only be reflective of the brain death pathophysiologic process. Regional wall motion abnormalities may not follow coronary supply distribution and hence are likely related to catecholamine injury. As this injury may be transient and wall motion abnormalities reversible, initial TTE should be delayed until the DBDD donor has been weaned off or to a minimal level of catecholamine hemodynamic support if possible. If performed early in the course of brain death, TTE should be repeated following aggressive donor management, at which time the findings may be a more accurate reflection of the true functional status of the myocardium and the suitability of the heart for transplantation. Transesophageal echocardiography (TEE) may be the modality of choice when TTE cannot be obtained because of chest wall abnormalities or if a more accurate assessment of cardiac function (particularly right ventricle) is warranted. TEE is also used when technical difficulties (body habitus, mechanical ventilation, lack of breath holding, or position readjustment) associated with TTE image acquisition are encountered.

Recommendations:

1. Hemodynamic assessments for brain-dead donors include serial determination and interpretation of
   a. Mixed venous oxygen saturation.
   b. Lactate.
   c. Base deficit and acid-base status.
   d. CVP, PAOP, or noninvasive hemodynamic parameters.
2. TTE is the preferred test to assess cardiac function in real time but may have limiting factors.
3. TEE provides superior image quality and assessment and should be done when TTE data are inconclusive or TTE cannot be performed adequately.
4. Echocardiography for determination of the suitability of the heart for transplantation ideally should be deferred until the donor has weaned off of catecholamines. If an echo performed early in the course of brain death demonstrates significant cardiac dysfunction, the echo should be repeated 12–24 hours following aggressive donor management.

ENDOCRINE DYSFUNCTION AND HRT

Endocrine abnormalities occur frequently with severe brain injury and brain death. Cerebral injury leads to brain edema and ischemia, which increases ICP. Brain death occurs when the elevation in ICP forces the brainstem to herniate through the foramen magnum, causing additional ischemic injury and ultimately brainstem infarction (135). The hypothalamic-pituitary axis is particularly vulnerable to ischemic injury. Reduction in vasopressin production leading to DI has been reported in up to 80% of patients with brain death (135–137). Anterior pituitary hormone deficits, resulting in hypothyroidism and hypocortisolism, have also been described, although at somewhat lower and variable rates (138). A number of preclinical and clinical studies have indicated that pharmacologic replacement of these hormones may promote hemodynamic stability, improve organ function, and increase the likelihood of multiple organ retrieval.

When Should Treatment for Vasopressin Deficiency Be Considered?

Damage to posterior pituitary structures, the hypothalamic supraoptic nuclei, and paraventricular nuclei results in low or undetectable levels of arginine vasopressin (AVP or antidiuretic hormone). AVP deficiency may lead to inappropriate diuresis and is associated with hypovolemia, hyperosmolality, and hypernatremia, findings consistent with DI (139). Additionally, even patients who do not meet criteria for DI appear to have impaired baroreflex-mediated secretion of AVP in response to hypotension and reduced circulating volume (140). Early intervention with appropriate therapy may restore

hemodynamic stability and prevent end-organ damage. A recent analysis of the OPTN database found that use of AVP in organ donors was independently associated with an increased rate of organ recovery (134). The study did not reveal the indications for AVP administration (e.g., hypotension and DI).

Several retrospective studies and one prospective study have reported that prolonged hypernatremia (Na+ > 155 mmol/L) resulting from untreated DI is associated with postoperative graft dysfunction after liver transplantation; however, this association has not been universally reported (141–144). Nevertheless, maintaining normal sodium levels is a reasonable treatment goal.

Excess diuresis, volume depletion, and hypernatremia may be due to causes other than DI (e.g., osmotic diuresis secondary to hyperglycemia or administration of mannitol) and must also be investigated.

Recommendations:

1. Treatment for AVP deficiency should be considered when hypotension persists despite adequate volume resuscitation.
2. Treatment for AVP deficiency should be considered in the presence of DI, which is likely to be present if one or more of the following criteria are identified in the absence of other causes of these abnormalities:
   a. Polyuria (urine output > 3–4 L/d or 2.5–3.0 mL/kg/hr).
   b. Normal or increased serum osmolality.
   c. Inappropriately dilute urine (specific gravity < 1.005, urine osmolality < 200 mOsm/kg H_2O).
   d. Hypernatremia (Na+ > 145 mmol/L).

How Should AVP Deficiency in the Organ Donor Be Treated?

The recommended pharmacologic agent for the treatment of AVP deficiency depends on the patient's clinical status. IV AVP replacement should be considered in the setting of neurogenic hypotension that persists despite adequate fluid resuscitation. This medication exerts several therapeutic effects by binding to three distinct G protein-coupled vasopressin receptors: V1 receptors on vascular smooth muscle mediate the pressor effect of AVP by inducing contraction of vascular smooth muscle; V2 receptors on the basolateral membrane of the distal nephron control aquaporins (water channels) in the renal collecting duct and promote an antidiuretic effect; V3 receptors, expressed in the anterior pituitary gland, bind to synergize with corticotropin-releasing hormone in regulating the production of adrenocorticotropic hormone (ACTH) (145). Several small retrospective studies investigating the use of AVP in potential organ donors and one randomized prospective study have shown that AVP administration is associated with improvement in blood pressure and reduced the requirement for catecholamine pressors and inotropes (131, 140, 146).

The ideal AVP dosing regimen for potential organ donors has not been clearly established. Some studies have suggested that the infusion rate in other types of vasodilatory shock (e.g., sepsis) should be restricted to a maximum of 0.03–0.04 IU/min due to concern that higher doses may be associated with adverse cardiac effects (147). However, a prospective study suggested that a much higher infusion rate (0.067 IU/min) was more effective at restoring cardiovascular and hemodynamic stability in advanced vasodilatory shock (148).

Desmopressin (1-deamino-8-D-arginine vasopressin) is a vasopressin analogue with significantly greater affinity for the V2 receptor than the V1 receptor. Thus, its primary biologic effect is antidiuretic; it appears to induce only a minimal vasopressor response (149). This agent is the drug of choice for the treatment of DI without associated hypotension and is used to control urine output and achieve serum sodium in the normal range. Dosing recommendations are somewhat empirical and depend on the patient's response. In practice, an initial desmopressin dose of 1–4 μg is administered IV. Urine osmolality, volume (goal < 4 mL/kg/hr), and serum sodium concentration are monitored closely to assess pharmacologic response and to avoid fluid retention and hyponatremia. When the output of dilute urine starts to increase, an additional dose of desmopressin is recommended. Typically 1–2 μg IV are required every 6 hours (137). Retrospective studies have suggested that desmopressin administration in the potential adult or pediatric organ donor with DI is associated with hemodynamic stability and perhaps increased yield of donor organs (150, 151).

Desmopressin increases concentrations of procoagulant factor VIII and von Willebrand factor and has been used as a hemostatic agent (152). Although the recommended dosing to induce procoagulant effects is significantly higher (0.3 μg/kg), concern has been raised that this medication may have detrimental thrombogenic effects on posttransplant graft function. Data from human studies are conflicting. A retrospective review of the Scientific Registry of Transplant Recipients database of over 2,800 patients who had undergone simultaneous kidney-pancreas transplantation showed an increased incidence of pancreatic graft thrombosis (5.1%) compared with the incidence in grafts from donors who did not receive desmopressin (3.1%) (153). In contrast, a prospective randomized investigation found no difference in early- or long-term function of kidneys recovered from donors who received desmopressin treatment compared with those who did not. Similarly, no impact on pancreatic function was noted in a single-center retrospective analysis (154, 155). More recently, retrospective analysis of a prospectively collected dataset from a clinical trial (evaluating donor pretreatment with dopamine) of almost 500 patients from over 60 European transplant centers reported no difference in early post–kidney transplant outcomes in the group that received desmopressin therapy but superior 2-year allograft survival, especially in the subset that also received dopamine therapy (130, 156). Other retrospective studies have similarly suggested benefit with regard to renal allograft function in association with donor desmopressin treatment (130, 156–158). Both AVP and desmopressin can be administered concurrently in the potential organ donor with significant hypernatremia and hypotension.

Recommendations:

1. If the donor is hypotensive and thought to have low systemic vascular resistance, start IV AVP at 0.01–0.04 IU/min. Higher doses can be tried with caution.

2. For DI with significant hypernatremia (sodium, > 145–150 mmol/L) without hypotension, treatment with desmopressin should be initiated. After an initial IV dose of 1–4 μg, additional dosing should be titrated to urine output, urine osmolality, and serum sodium. Typically, an additional 1 or 2 μg every 6 hours will be required, although higher doses can be used safely.
3. Both AVP and desmopressin can be used concurrently in the hemodynamically unstable donor with severe hypernatremia.
4. Electrolytes should be monitored closely as urinary losses associated with DI can lead to hypokalemia, hypophosphatemia, and hypomagnesemia. These electrolytes should be replenished.

When Should Treatment With Corticosteroids Be Considered?

The prevalence of corticosteroid deficiency has been reported at variable rates after brain death. This variability is due in part to the definition used to identify these patients (136, 137, 159, 160). In a review of 32 consecutive brain-dead organ donors, all but one patient had detectable cortisol levels. Interestingly, all patients who had received dexamethasone ($n = 11$) before brain death for treatment of brain injury had random cortisol levels less than 10 μg/mL, suggesting that adrenal suppression was common in this subgroup. ACTH levels were not reduced in this study (137). In a more recent investigation of 37 consecutive patients with severe brain injury, patients who progressed to brain death had lower random cortisol levels and were less likely to respond to a physiologic dose (1 μg IV) of ACTH, suggesting that there is an increased risk of relative adrenal insufficiency in the brain-dead organ donor (138). The physiologic consequences of relative corticosteroid deficiency, however, remain uncertain. In this study, hemodynamic parameters and inotrope requirements were not different in brain-dead patients with and without relative adrenal insufficiency. Thus, the recommendation to treat potential donors with corticosteroids is not based on strong evidence that clinically significant hypocortisolism is present.

In addition to hemodynamic instability and hormonal imbalances, brain death also triggers a cascade of events that leads to upregulation of proinflammatory and immunologic mediators. This response has been associated with reduced graft function after transplantation (161, 162). Treatment of the donor with high doses of corticosteroids to reduce brain death-induced inflammation and modulate immune function may improve donor organ quality and posttransplant graft function. For example, a prospective randomized controlled trial of 100 brain-dead donors showed that the 50 donors who received treatment with methylprednisolone (250 mg IV followed by an infusion of 100 mg/hr until organ recovery) had significantly lower levels of proinflammatory cytokines in the serum. Liver biopsy findings revealed reduced expression of inflammatory cytokines and adhesion molecules in the graft, and severity of ischemia-reperfusion injury and acute rejection rates were lower in patients who had received organs from donors treated with corticosteroids (163). Although some studies have reported that preprocurement donor treatment with corticosteroids either alone or as part of a combination regimen may have beneficial effects on graft function after renal and cardiac transplantation, a randomized prospective multicenter study did not demonstrate a reduction in the frequency or duration of posttransplant acute renal failure in treated patients (135, 164–166).

In a retrospective study, donor treatment with high doses of methylprednisolone was reported to be associated with improved donor lung quality (higher Pao_2/Fio_2 ratios) and increased organ retrieval rates (167). A follow-up study several years later showed that methylprednisolone treatment was an important independent predictor of successful lung donation (168). However, a randomized prospective study evaluating the role of aggressive donor management strategies failed to show additional benefit from steroid administration on lung retrieval rates, oxygenation, or levels of serum proinflammatory cytokines. Corticosteroid use was associated with reduced extravascular lung water accumulation. Corticosteroid use did not lead to improved donor cardiac function or higher retrieval rates (133, 169, 170).

Recommendation:

1. High-dose corticosteroid administration (methylprednisolone 1,000 mg IV, 15 mg/kg IV, or 250 mg IV bolus followed by infusion at 100 mg/hr) reduces the potential deleterious effects of the inflammatory cascade on donor organ function following brain death. Ideally it should be administered after blood has been collected for tissue typing as it has the potential to suppress human leukocyte antigen expression.

When Should Thyroid Replacement Therapy Be Considered?

Most of the evidence supporting use of thyroid replacement therapy has come from investigations in animal models demonstrating significant decline in triiodothyronine (T3) and free thyroxine (T4) levels after brain death (159, 171, 172). Preclinical studies have suggested that pituitary hormone deficiency, especially hypothyroidism, is associated with depleted myocardial energy stores, a shift from aerobic to anaerobic metabolism and reduced cardiac function. Treatment with a combination hormone therapy regimen that included T3 reversed the cardiac dysfunction seen after brain death, and T3 alone was able to restore aerobic metabolism (159, 173). These observations have led to increased interest in the clinical application of thyroid hormone replacement as a therapeutic approach to promote hemodynamic stability and improve cardiac function.

In humans, reduced levels of thyroid hormone and thyroid-stimulating hormone (TSH) have not been consistently reported after brain death (136, 137, 160, 174, 175). Even when present, low levels of circulating thyroid hormone are not always associated with hemodynamic instability. Studies have suggested that the abnormal thyroid function values seen after brain death are more consistent with the sick euthyroid syndrome rather than true hypothyroidism (176, 177). For example, in a prospective study of 31 consecutive organ

donors, 81% had subnormal T3 values. Reverse T3 levels were normal or elevated in every case. Serum T4 levels were reduced in only 29%, and serum TSH levels were abnormal in 23% of the cases. Notably, none of these patients had both reduced T4 and TSH levels, supporting a diagnosis of sick euthyroid syndrome rather than true TSH deficiency (136).

One approach to assessing the clinical significance of hypothyroidism has been to empirically treat brain-dead organ donors with thyroid hormone. In one of the earliest studies to investigate the role of thyroid replacement in clinical practice, 21 brain-dead donors who received hormone therapy including T3 (in addition to IV cortisol and insulin) were compared with 26 donors who did not receive this therapy. The group receiving therapy was noted to have significant improvement in cardiovascular status and a reduced requirement for inotropic support. Additionally, fewer donors were deemed unsuitable for heart donation compared with those who received only conventional therapy (178). Recommendations for routine administration of thyroid hormone as part of donor management protocols have sparked considerable debate in the transplant community as its positive effects have not been reported in all studies (165, 176, 179–183). The most convincing data pertain to cardiac function and heart transplantation, but conflicting reports exist even in this area (133, 159, 176, 183–186). For example, in a prospective randomized, blinded, placebo-controlled study of 37 brain-dead patients, thyroid hormone treatment did not improve hemodynamic status or cardiac function (176). One author has suggested that thyroid hormone replacement may only be needed for hemodynamically unstable donors (187). Alternatively, perhaps only patients with true hypothyroidism will benefit as many brain-dead donors do not have total absence of anterior pituitary function. Finally, heterogeneity in study design, utilization of varying dosages of thyroid hormone, and combination with other agents may also contribute to the differing results (188).

Several studies, including data from UNOS, have found that thyroid hormone therapy, in addition to AVP and methylprednisolone, significantly increases the probability of successful organ recovery and may be associated with improved cardiac recipient survival, although this finding also has not been universally confirmed (133, 164, 165).

Recommendation:

1. Thyroid replacement therapy—either alone or as part of a combination hormone therapy with IV AVP, corticosteroids, and insulin—should be considered for hemodynamically unstable donors or for potential cardiac donors with abnormal (< 45%) left ventricular ejection fraction.

How Should Thyroid Hormone Replacement Be Administered?

Both T3 and T4 have been used to treat brain-dead organ donors. T4 is typically converted to the more biologically potent T3 in the body. Thus, T3 has a more rapid onset of action and is not vulnerable to exogenous factors that interfere with conversion of T4 to T3. The concern regarding T4 administration may be overcome by administering larger doses. Data from UNOS have not shown an obvious difference in effectiveness between T3 and T4 (159, 180, 189).

Recommendation:

1. Both T3 and T4 are acceptable for use as a component of HRT. One commonly utilized protocol is as follows: administer T4 IV with a 20-μg bolus, followed by an infusion at 10 μg/hr, or administer T3 IV with a 4.0-μg bolus, followed by an infusion at 3 μg/hr.

Should Deceased Organ Donors With Hyperglycemia Be Treated?

Although hyperglycemia in critically ill patients is extremely prevalent, its occurrence in deceased organ donors is less well documented in the literature. Brain death causes major hormonal alterations that result in insulin resistance and gluconeogenesis. Furthermore, the practice of administering dextrose-containing solutions may worsen glucose homeostasis. In a retrospective study of 458 deceased organ donors from a single OPO, terminal glucose concentrations prior to organ recovery were significantly higher than recommended ICU practice standards. Seventy-two percent of the donors had terminal glucose concentrations more than 200 mg/dL and 39% had glucose concentrations more than 250 mg/dL (157).

The impact of hyperglycemia on organ donor function is uncertain. Hyperglycemia-associated osmotic diuresis may lead to volume depletion and electrolyte abnormalities and perhaps increase the risk of donor organ dysfunction, but data are scant. In the retrospective study of deceased organ donors, higher glucose levels and greater fluctuations in levels were associated with reduced prerecovery renal function (157). A small prospective study of 40 recipients of living donor renal transplants showed that intraoperative hyperglycemia (blood glucose, > 160 mg/dL) was associated with reduced early post-transplant renal function (190).

The concern that hyperglycemia may induce overstimulation and metabolic exhaustion of pancreatic islet cells, with potential detrimental effect on donor cell function, must be further explored (191–194). Any impact on other types of organs is notably absent. Results of a prospective randomized clinical trial (ClinicalTrials.gov identifier: NCT01140035) on the effect of conventional and intensified insulin administration on renal allografts from deceased organ donors are expected in the near future. Preliminary analysis of this study revealed no difference in terminal creatinine between the two treatment groups. When glucose was used as a continuous variable, a strong association was again found between glucose concentrations and terminal creatinine. The negative study results may in part be due to the excellent glucose control in the conventional treatment arm, with a target glucose concentration of 180 mg/dL (C Niemann, personal communication, 2012).

Hyperglycemic deceased organ donors should be treated as other critically ill patients. Although there remains considerable debate regarding target glucose levels for intensive insulin therapy in critically ill patients, it is generally accepted that uncontrolled hyperglycemia should be treated. Most ICUs

have adopted empiric protocols with target glucose levels less than 180 mg/dL, which appears to be appropriate for deceased donors as well (195). Modifications of institutional ICU guidelines for glucose management should be incorporated into OPO protocols. Finally, the practice of routine administration of IV fluids containing dextrose should be reassessed.

Recommendations:

1. Hyperglycemic organ donors should be managed according to institutional guidelines for other critically ill patients.
2. Routine use of IV fluids containing dextrose should be avoided.

PEDIATRIC DONOR MANAGEMENT ISSUES

See online supplement I (Supplemental Digital Content 1, http://links.lww.com/CCM/B250) for background information on pediatric donor management issues.

Should Potential Pediatric Organ Donors Be Managed in Specialized ICUs?

Organ donation and transplantation in children has unique characteristics. These include, but are not limited to, 1) size and weight constraints that can limit organ recovery and utilization; 2) technical challenges related to surgical procedures in small infants; 3) age-related variation in the declaration of death by neurologic criteria, resulting in deterioration of organ viability; 4) absence of the specialized care required for management of critically ill children and pediatric donors; and 5) parent or guardian authorization because child donors cannot express their wishes regarding organ donation. These unique issues require that nursing and critical care specialists have expertise in the management of critically ill children and their families. Support may also be needed from neurologists, neurosurgeons, general surgeons, and other pediatric subspecialists. These and other resources may not be available in some hospitals.

Recommendations:

1. If a child with a life-threatening condition is admitted to a hospital where pediatric support is not readily available, every effort should be made to transfer the child to a center equipped to manage these issues.
2. If transfer to a pediatric center is not an option, pediatric critical care resources in the community should be consulted to provide the needed expertise to assist with pediatric donor management.

What Are the Unique Aspects of Declaration of Brain Death in the Pediatric Population?

Accurate determination of death is essential before efforts to recover organs can proceed. Brain death must also be declared in a timely and efficient manner for several reasons: it allows families to begin the grieving process; it prevents caregivers from wasting valuable resources; and it allows the focus to shift to care and preservation of organ system function if authorization for donation occurs. Up to 25% of potential donors can be lost to hemodynamic instability and organ dysfunction if appropriate care is not maximized (196–198). Additionally, institution of early and aggressive HRT may improve graft function postoperatively (164, 165, 179, 198–200).

Guidelines for the determination of brain death in children were published by a special task force in 1987 and revised recently by the SCCM, American Academy of Pediatrics, and Child Neurology Society (201–204) to include six key recommendations.

Recommendations:

1. Determination of brain death in term newborns, infants, and children is a clinical diagnosis based on the absence of neurologic function with a known irreversible cause of coma.
2. Hypotension, hypothermia, and metabolic disturbances should be treated and corrected. Medications that can interfere with the neurologic examination and apnea testing should be discontinued allowing for adequate clearance before proceeding with these evaluations.
3. Two examinations, including apnea testing with each examination separated by an observation period, are required. Recommended observation periods are 24 hours for term newborns (37-wk gestational age) and infants through 30 days old and 12 hours for infants and children (> 30 d to 18 yr). The first examination determines the child has met the accepted neurologic examination criteria for brain death; the second confirms brain death based on an unchanged and irreversible condition. Assessment of neurologic function after cardiopulmonary resuscitation or other severe acute brain injuries should be deferred for more than 24 hours if there are concerns or inconsistencies in the examination.
4. Apnea testing to support the diagnosis of brain death must be performed safely and requires documentation of an arterial $Paco_2$ 20 mm Hg above the baseline and more than 60 mm Hg with no respiratory effort during the testing period. If the apnea test cannot be safely completed, an ancillary study should be performed.
5. Ancillary studies (electroencephalogram and radionuclide cerebral blood flow) are not required to establish brain death and are not a substitute for the neurologic examination. These studies may assist the clinician in making the diagnosis of brain death in the following situations: when components of the examination or apnea testing cannot be completed safely; if the results of the neurologic examination are uncertain; if a medication effect may be present; or if the interexamination observation period is reduced. When ancillary studies are used, a second clinical examination and apnea test should be performed, and components that can be completed must remain consistent with brain death.
6. Death is declared when these criteria are fulfilled.

These updated guidelines for the determination of brain death in infants and children have improved clarity in the determination of death in children (202, 203).

Recommendations:

1. The clinician must understand the etiology of the child's neurologic demise. The younger the child, the more caution needed in determining death by neurologic criteria.

Concerns regarding the determination of death call for ancillary studies and reexamination of the child following a longer observation period.

2. Determination of brain death in children should be based on accepted guidelines. Physicians should become familiar with any revised guidelines to ensure that death is declared by accepted medical standards.

What Strategies Should Be Utilized in Managing the Potential Pediatric Organ Donor?

Once death has been declared and authorization for organ donation obtained, care shifts toward preservation of organ function with a goal of restoring normal hemodynamics, ventilation, and oxygenation. This can improve graft function for the transplant recipient, potentially shorten hospital stay, and decrease morbidity and mortality (151). The severe cardiovascular derangements associated with neurologic death require support in the form of volume resuscitation and inotropic agent administration. Vasoactive agents, such as dopamine, epinephrine, and norepinephrine, are frequently utilized to maintain hemodynamic stability in these very unstable children (6, 204, 205). A strategy to maintain blood pressure, normovolemia, and optimization of CO using the least amount of vasoactive agents has been adopted by many pediatric centers and OPOs involved in organ recovery (198, 204). Donor management goals should restore normal blood pressure for age, normal ventilation and oxygenation parameters, and normal fluid balance and electrolyte values (**Table 5**). Although supporting evidence is lacking in children, HRT is commonly used to balance the use of inotropic agents and fluids and maintain the viability of organ function.

Loss of adrenal and thyroid hormone secretion resulting in fluid and electrolyte disturbances occurs from dysfunction of the neurohumoral axis. These disturbances will alter hemodynamics if not aggressively managed in the potential donor. Pharmacologic agents to control DI must be used in conjunction with volume replacement therapy to maintain a euvolemic state and prevent the significant fluid losses that can grossly alter hemodynamics and electrolyte balance, which would render donor organs unsuitable for transplantation. Although DI does not occur in all patients declared dead by neurologic criteria (206), those with it can have profound fluid and electrolyte disturbances if aggressive therapy with fluid replacement and use of vasopressin or desmopressin are not utilized to control excessive urine output. In one study, use of vasopressin was shown to reduce the need for inotropic support without affecting graft function (146).

Thyroxine and T3 are the two IV agents available to replace the loss of circulating thyroid hormone that can occur with brain death. Levothyroxine is commonly used by many centers to provide pharmacologic support for altered hemodynamics, in conjunction with fluids and inotropic support. Some centers use T3, but the cost of this agent may be prohibitive. Although pediatric studies are limited, use of thyroid hormone in children declared dead by neurologic criteria has been shown to decrease the need for inotropic support in this population (207). It seems reasonable to consider these agents when hemodynamic status is refractory to conventional therapy with fluid and inotropic administration (180, 187, 199, 200). Thyroid hormone has also been associated with an increase in transplanted organs from adults receiving HRT, but no studies in children have been published (164, 165, 208).

Steroid therapy is employed by many OPOs to augment or replace steroid production as a result of the adrenal dysfunction that occurs with brain death. Methylprednisolone is commonly used to assist with hemodynamic support, even though few data attest to its benefits in the potential pediatric organ donor (205). Bolus or continuous infusion dosing of

TABLE 5. Pediatric Donor Management Goals

Hemodynamic support		
Normalization of blood pressure		
Systolic blood pressure appropriate for age		
Lower systolic blood pressures may be acceptable if biomarkers such as lactate are normal		
Central venous pressure < 12 mm Hg		
Dopamine < 10 μg/kg/min		
Normal serum lactate		
Blood pressure	Systolic (mm Hg)	Diastolic (mm Hg)
Neonate	60–90	35–60
Infants (6 mo)	80–95	50–65
Toddler (2 yr)	85–100	50–65
School age (7 yr)	90–115	60–70
Adolescent (15 yr)	110–130	65–80
Fluids and electrolytes		
Serum Na^+	130–150 mEq/L	
Serum K^+	3–5.0 mEq/L	
Serum glucose	60–150 mg/dL	
Ionized Ca^{++}[a]	0.8–1.2 mmol/L	
Oxygenation and ventilation		
Maintain Pao_2, > 100 mm Hg		
Fio_2, 0.40		
Normalize $Paco_2$, 35–45 mm Hg		
Arterial pH, 7.30–7.45		
Tidal volumes, 8–10 mL/kg		
Positive end-expiratory pressure, 5 cm H_2O		
Thermal regulation		
Core body temperature 36–38°C		

[a]Calcium can improve blood pressure in neonates and infants

Modified with permission from Nakagawa TA: North American Transplant Coordinators (NATCO) Donor Management and Dosing Guidelines. Available at: http://www.organdonationalliance.org/wp-content/uploads/toolbox.v.2/NATCOPedDonorManagementGuidelines1-odt.pdf. Accessed March 1, 2015.

methylprednisolone can play an important role in stabilization of function in the potential lung donor (122). The clinical benefits of steroids remain untested in the pediatric population.

HRT may provide stabilization of the potential donor, thus preventing a rushed approach to organ recovery and placement. Although HRT is widely practiced despite lack of convincing evidence, the combination of thyroid hormone and steroids may be used as pharmacologic adjuncts to reduce vasoactive agents in children requiring high-dose inotropic support. Additionally, vasopressin may assist with control of DI and further reduce the need to for inotropic support (99). HRT may improve successful organ recovery for children, but further studies are clearly warranted.

Specific HRT agents and pediatric doses are outlined in **Table 6**.

Recommendations:

1. Donor management goals should focus on normalizing and maintaining hemodynamic stability, oxygenation and ventilation, and fluid and electrolyte balance to preserve organs for transplantation.
2. Limited evidence shows the use of thyroid hormone, and vasopressin for the management of DI, can reduce the need for inotropic support in the pediatric donor. Initiating HRT may improve graft function and preserve donor stability prior to organ recovery. No published reports indicate that HRT has deleterious effects in children. Based on this premise, early initiation may be beneficial and should be strongly considered.

Does Referral of a Pediatric Victim of Nonaccidental Trauma to the Medical Examiner Preclude Consideration of Organ Donation?

Nonaccidental trauma that has resulted in the death of a child requires close cooperation between forensic investigators, treating physicians, the transplant team, and OPO to allow for successful organ recovery (209–215). However, despite encouragement from medical examiners, denials for organ donation continue to occur (216). Protocols to facilitate organ recovery in child abuse victims can decrease denials from medical examiners (217, 218). Involvement of the district attorney and medical examiner/coroner in protocol development should be considered.

Recommendations:

1. Collaboration between physicians, transplant specialists, the OPO, and medical examiners is required for successful recovery of organs and successful prosecution of child abuse cases. Involvement of the pediatric forensic team is essential in suspected or confirmed cases of child abuse.
2. Protocols should be developed to reduce or eliminate medical examiner and coroner denials.

Are There Special Considerations in Obtaining Family Authorization for Pediatric Organ Donation?

Increasing evidence reveals that authorization for pediatric organ donation is augmented by involvement of the pediatric intensivist and the specialized care provided by the staff in the PICU (219–223). Collaboration with the OPO and the PICU team is paramount to provide support and guidance to the family during end-of-life decisions. The unique issues surrounding the death of a child require trained staff members who are familiar with the needs of the family (219–222).

Recommendations:

1. OPO coordinators should routinely consult with the pediatric intensivist and PICU team to determine the best approach to requesting organ donation from families of children.
2. As a trusted member of the medical team, the pediatric intensivist should be involved in discussions with the family about donation.
3. The child's primary care provider may also be a valuable resource for discussions about organ donation.

TABLE 6. Pharmacologic Agents for Pediatric Hormonal Resuscitation

Drug	Dose	Route	Comments
Desmopressin	0.5 μg/hr	IV	Half-life 75–90 min; titrate to decrease urine output to 3–4 mL/kg/hr; may be beneficial in patients with an ongoing coagulopathy
Arginine vasopressin	0.5 mU/kg/hr	IV	Half-life 10–20 min; titrate to decrease urine output to 3–4 mL/kg/hr; hypertension can occur
Thyroxine (T4)	0.8–1.4 μg/kg/hr	IV	Bolus dose 1–5 μg/kg can be administered; infants and smaller children require a larger bolus and infusion dose
Triiodothyronine (T3)	0.05–0.2 μg/kg/hr	IV	Dose may be repeated in 8–12 hr
Methylprednisolone	20–30 mg/kg	IV	Fluid retention; glucose intolerance
Insulin	0.05–0.1 U/kg/hr	IV	Titrate to control blood glucose to 60–150 mg/dL; monitor for hypoglycemia

Treatment of diabetes insipidus should consist of pharmacologic management to decrease but not completely stop urine output. Replacement of urine output with 0.25% or 0.5% normal saline should be used in conjunction with pharmacologic agents to maintain serum sodium levels between 130 and 150 mEq/L. Hormone replacement therapy should be considered early in the course of donor management. Its use may allow weaning of inotropic support and assist with metabolic stability for the pediatric donor.

Modified with permission from Nakagawa and Mou (204).

Is DCDD an Acceptable Means of Procuring Organs From Pediatric Donors?

The number of organs recovered from DCDD pediatric donors continues to increase, accounting for approximately 10% of all DCDD donors nationally (224, 225). This population represents an important area of growth for donation (50, 51, 226, 227). Organs from pediatric DCDD donors are being recovered and transplanted with good success (228). Three neonatal hearts were recovered and transplanted under a research protocol (229). Organs recovered from infant DCDD donors have the potential to further increase organs available for transplantation (230, 231). Many pediatric hospitals have developed DCDD policies, but considerable variation among policies exists (232). The American College of Critical Care Medicine and the American Academy of Pediatrics support DCDD as an acceptable method for recovering organs when performed within the specific boundaries outlined in their position statements (209, 233).

Recommendations:

1. Use of DCDD pediatric donors is recommended when performed according to strict protocols.
2. Continued research is needed within the pediatric transplantation community to study the long-term impact of transplanted organs, patient outcomes, and staff perspectives related to DCDD donors (232–237).
3. Efforts should be made to standardize DCDD protocols for determination of death and recovery of organs from the pediatric population.
4. Organ recovery from neonatal donors should be considered to increase the pool of organs available for transplantation.

Should Anencephalic Infants Be Considered for Organ Donation?

The use of anencephalic infants as organ donors has raised significant ethical concerns (238–240). These infants cannot be organ donors in the United States because they do not meet brain death criteria. Organs from these donors have, on rare occasion, been transplanted into other children (241). Recovery of organs from DCDD anencephalic donors may be limited by size constraints, difficulty in placing organs, and uncertainty whether the infant will proceed to cardiorespiratory death within the specified time for viability.

Recommendation:

1. Anencephalic infants may be considered for organ donation; however, more research and experience are needed in this area.

ORGAN SYSTEM-SPECIFIC CONSIDERATIONS

Cardiac Donors

Are There Any Unique Selection Criteria Regarding the Cardiac Donor? In addition to the usual exclusion criteria applied to all organ donors, traditional exclusion criteria specific to heart donation have included the presence of functional and morphologic cardiac disease, advanced donor age, mismatch of donor/recipient size, previous cardiac arrest, and significant thoracic trauma with particular emphasis on myocardial contusion (242, 243). However, the growing number of patients with heart failure has led to estimates that 20,000–30,000 patients each year might benefit from cardiac transplantation (244). This demand grossly exceeds the number of hearts deemed suitable by traditional criteria, typically between 2000 and 2400 per year (245). In the face of this severe shortfall, strategies to extend the criteria for donor suitability and better manage the multiple organ donor have been implemented to expand the pool of available hearts. Data have revealed that such an expansion of traditional criteria has been associated with good outcomes (246). A detailed discussion of extended donor criteria is in online supplement I (Supplemental Digital Content 1, http://links.lww.com/CCM/B250).

Recommendations:

1. It is acceptable to expand the age of donors to 55 years. Although donors beyond this age could be considered, the increased recipient mortality associated with older donors must be considered.
2. Mild donor left ventricular hypertrophy (wall thickness < 1.4 cm) is acceptable.
3. Donors experiencing a cardiac arrest of up to 20 minutes, followed by "successful" resuscitation, can be considered for cardiac donation.
4. If the potential recipient has significant pulmonary hypertension, undersizing of the donor heart (i.e., using a donor with a body mass index [BMI] < 80% of recipient BMI) should be avoided.
5. Data are lacking regarding the use of hearts from donors with thoracic trauma. If a donor is considered under these circumstances, a thorough examination of the explanted heart should be performed immediately in the operating room.

Is There Any Value to Monitoring Cardiac Enzymes? Creatine phosphokinase values are nonspecific, and assessment is confounded by the acute trauma that led to brain death (247). Cardiac troponin levels (troponin T or I) have greater sensitivity and specificity for myocardial injury (248). One study suggested that the assessment of isoform might be useful in the evaluation of a marginal (i.e., extended criteria) heart donor and might serve as a prognostic indicator of posttransplant myocardial outcome (249), but other studies have demonstrated conflicting data, finding no clear relationship (250, 251). Furthermore, there appears to be no threshold value above which a heart with normal echocardiographic parameters could not be utilized nor does serial evaluation of troponin I levels appear to hold any value (252, 253). Thus, no specific recommendations for monitoring of cardiac enzymes were made by the cardiac working group at the Crystal City Consensus Conference (189). The more recent Canadian consensus statement recommended routine monitoring of troponin values but cautioned clinicians as to their limited role in making decisions about individual heart donors (6).

Recommendation:

1. Conflicting data and lack of consensus preclude firm recommendations on the utility of monitoring cardiac enzymes in the decision to use heart donors.

Is There Any Value to Monitoring B-type Natriuretic Peptide Levels? B-type natriuretic peptide (BNP) has prognostic and severity-of-illness implications in diseases, such as acute myocardial infarction and pulmonary embolus, but its role in selecting heart donors is uncertain. A preliminary study found that BNP levels were significantly lower in donors with hearts considered acceptable for transplantation compared with those whose hearts were unsuitable (254).

Recommendation:

1. No recommendations regarding the use of BNP levels can be made.

What Is the Role of Diagnostic Imaging in Evaluating the Cardiac Donor? The two principal imaging modalities for evaluating the potential heart donor are echocardiography and coronary angiography. TTE permits an extensive evaluation of structural and functional aspects of individual hearts, describing wall motion and thickness, chamber size, and valvular integrity and function. Echocardiography can be done at the bedside, and its noninvasive nature facilitates repeatability. This last feature has been invaluable in recognizing that transient myocardial dysfunction, commonly encountered early in the course of brain death, often can be fully reversed with aggressive donor management strategies (181). Views obtained from TTE may be obscured in a broad chest or by abdominal bandages, thoracostomy tubes, and mechanical ventilators, making TEE useful. The transplant, cardiology, and critical care communities of both the United States and Canada have incorporated the use of serial echocardiograms into treatment strategies for early cardiac dysfunction following brain death (6, 189).

Coronary angiography confirms the absence of relevant occlusive disease in the evaluation of both older donors (older than 40 yr) and younger donors with additional risk factors for premature coronary artery disease (6, 189). In one series, clinically relevant coronary artery disease (defined as > 50% stenosis) was found in 6.5% of donors age 40–49 years and 7.3% of those age 50–59 years (255). Multivessel coronary disease is associated with a high risk of early graft failure (256). Cardiac catheterization provides information regarding wall motion. Importantly, the administration of contrast media in coronary angiography has not been associated with impairment of donor kidney function, especially if the usual recommendations to diminish this risk are observed (257). The expense of coronary angiography is offset by the potential to obviate unnecessary mobilization of transport teams and unnecessary travel (258).

Recommendations:

1. Echocardiography should be performed whenever the heart is under consideration for transplantation.
2. Serial echocardiograms should be performed to monitor the response to medical management when early cardiac dysfunction is identified in potential donors.
3. Coronary angiography is recommended in the evaluation of older donors (> 40 yr) and younger donors with risk factors for premature coronary artery disease to confirm the absence of clinically relevant occlusive disease.

Are There Any Specific Recommendations Regarding Arrhythmia Management? A wide variety of arrhythmias are encountered in severely injured patients, especially those with severe brain injury or other acute catastrophic intracranial events. These arrhythmias may result from direct cardiac injury (e.g., myocardial contusion or pericarditis from thoracic trauma) or ischemic injury from a cardiac arrest. Other contributing factors are electrolyte imbalances and hypothermia. Additionally, the spectrum of altered adrenergic responses seen in the course of brain death predisposes the potential organ donor to a myriad of transient and sustained arrhythmias requiring medical management (259, 260). No literature specific to this population affords recommendations. In general, it is prudent to follow the established advanced cardiopulmonary life support guidelines. The autonomic storm, usually 15–30 minutes, can occasionally last several hours, after which cardiovascular collapse ensues (261). Recognizing this, the initial approach should include avoidance of overreaction and the use of short-acting agents. Bradyarrhythmias are the consequence of high-level vagal stimulation and exhibit a high degree of resistance to atropine; β-agonists and occasionally transvenous pacing are required (262). Ventricular arrhythmias encountered in hypothermia similarly exhibit a high degree of refractoriness to conventional therapy and improve with rewarming.

Recommendations:

1. The established advanced cardiopulmonary life support guidelines should be followed to manage arrhythmias.
2. Treatment with short-acting agents is preferred in tachyarrhythmias, given the dynamic changes in autonomic dysfunction.

What Is the Role of HRT in the Management of the Potential Cardiac Donor? The ischemic injury incurred by the hypothalamic-hypophyseal axis has been postulated to lead to a progressive deficiency in endogenous hormones produced in these regions. Studies have revealed a decline in myocardial energy substrates and an accumulation of tissue lactate, suggesting a change from aerobic to anaerobic metabolism as a consequence of deficiencies in T4, cortisol, and insulin and their roles in regulating cellular respiration (178).

Recommendation:

1. HRT is recommended for potential cardiac donors with evidence of left ventricular dysfunction. See the *Endocrine Dysfunction and HRT* section for details.

Kidney Donors

Are There Any Unique Selection Criteria Regarding the Kidney Donor? The kidney donor risk index provides transplant surgeons and physicians with a score evaluating the relative risk of graft loss based on specific donor variables (263). This score (on a continuum) should be used to help counsel the recipient on the merits of accepting a kidney with predicted poorer longevity balanced by the potential for receiving the kidney at an earlier time. Similar to trends seen with other solid-organ donors, there has been increasing use of kidney donors that do not meet

standard selection criteria. A discussion of extended criteria considered to be acceptable and criteria considered to be more problematic can be found in online supplement I (Supplemental Digital Content 1, http://links.lww.com/CCM/B250).

Recommendation:

1. Recognizing that many donors who do not meet standard selection criteria are still suitable to donate kidneys, members of the ICU team should discuss the particular details of each case with the OPO representative.

What Is the Role of Biopsy in the Potential Kidney Donor? In general, the benefit of kidney preprocurement biopsies is outweighed by the risk of bleeding, and biopsy is not routinely indicated. However, results of a kidney biopsy in potential extended criteria donors can help assess glomerulosclerosis, interstitial fibrosis, and vascular changes, factors in the kidney's suitability for transplantation (264–267).

Recommendations:

1. Routine biopsy is not indicated in standard criteria donors with normal creatinine.
2. Biopsy should be considered in the evaluation of certain extended criteria donors.

Is There a Role for Preprocurement Radiographic Imaging of the Potential Donor's Kidneys? No clear consensus or clear recipient benefit exists for any radiographic study before donation of kidneys from deceased donors. Such studies should be considered in potential donors with a history of familial polycystic kidney disease, kidney stones, or urologic abnormalities (15, 264, 267–269).

Recommendation:

1. Routine radiographic assessment of the deceased kidney donor is unnecessary, but should be considered for potential donors with
   a. Family history of polycystic kidney disease
   b. History of kidney stones
   c. History of urological anomalies

Can a Kidney Be Accepted From a Donor Who Has Received IV Contrast? The literature supports the use of kidneys from donors who have received IV contrast. No significant increase in the prevalence of delayed graft function or reduction in graft survival has been associated with perimortem donor contrast studies (257, 269, 270).

Recommendations:

1. Donors who have received contrast for radiographic studies may be suitable kidney donors.
2. If any radiographic studies requiring contrast are deemed to be absolutely necessary, the donor should first be adequately hydrated, with brisk diuresis established, and the minimal amount of contrast necessary to achieve an adequate study should be used.

Is There an Optimal Fluid Resuscitation Strategy to Improve the Function of Kidney Grafts? Most studies investigating renal graft function in resuscitated brain-dead organ donors are either retrospective case series or uncontrolled observational studies. Appropriate management of DI, restoration of adequate intravascular volume, and correction of acidosis were all associated with lower rates of delayed graft function and improved serum creatinine levels prior to organ recovery (151, 158, 271, 272).

Recommendation:

1. IV fluids should be administered to maintain euvolemic volume status and address ongoing fluid losses and electrolyte disturbances associated with DI.

Does the Use of Colloids in the Resuscitation of Brain-Dead Donors Improve Renal Graft Function? Studies examining the role of colloids in preserving renal graft function mainly focused on the use of HES compared with albumin or gelatin infusions. The only prospective randomized controlled trial of colloids and their effect on deceased donor renal graft function involved 27 donors and compared a standardized resuscitation strategy with gelatin plus large molecular–weight HES (200 kDa) with gelatin alone (273). Delayed graft function was significantly higher in the HES group (33% vs 5%) as was the average 10-day recipient serum creatinine level. Subsequent retrospective studies have revealed the following mixed results: 1) HES does not decrease renal graft function (274); 2) increased volumes of non-HES colloids decrease delayed graft function (275); 3) albumin infusions lower creatinine levels prior to organ recovery compared with HES (276); and 4) low-molecular-weight HES (130 kDa) leads to lower 1-month and 1-year recipient creatinine levels compared with 200 kDa HES (125).

Recommendations:

1. No recommendation can be made on selecting between a colloid and a crystalloid resuscitation strategy because evidence of the effect on renal graft function is insufficient.
2. The use of HES generally appears to worsen outcomes compared with other colloids and is therefore not recommended in organ donors.

What Is the Effect of Vasopressors and Inotropic Agents on Kidney Graft Function? Evidence is based on retrospective studies (157, 158, 277) with the exception of one prospective randomized trial (130). All common vasopressors—dopamine, dobutamine, phenylephrine, epinephrine, and norepinephrine—are used in the management of organ donors, but the first choice in vasopressors is inconsistent. Norepinephrine was used as a first-line vasopressor (71%) in one study ($n = 143$) (158), whereas phenylephrine (85%) was the preferred choice elsewhere ($n = 458$) (157). Similar divergence can be observed for use of epinephrine and dopamine.

In terms of the effects on kidney grafts, the use of catecholamines in the donor has been associated with improved allograft survival (277). However, one retrospective study identified epinephrine use as an independent factor for elevated creatinine levels prior to organ recovery (158). A randomized, open-label study demonstrated that the infusion of low-dose dopamine (4 μg/kg/min) in the donor reduced the need for posttransplant dialysis in the recipient (130). AVP is increasingly used

in organ donor management to treat both DI and hypotension, but published results of its use are not available. A recent large retrospective study demonstrated that the use of AVP resulted in increased organ procurement, including kidneys (134).

Recommendation:

1. Based on limited evidence, selective use of vasopressors and inotropes is justified in the resuscitation of deceased kidney donors.

Liver Donors

What Are the Selection Criteria for Liver Donors? The severe shortage of organs available for transplantation and the high mortality among patients on the liver waiting list (113 deaths per 1,000 patient-years at risk) have led to liberalizing selection criteria (278, 279). Although the OPO and transplant team make the final determination of organ suitability, the critical care physician should be aware of the liberalized criteria. A detailed discussion of these criteria is available in online supplement I (Supplemental Digital Content 1, http://links.lww.com/CCM/B250).

Recommendations:

1. Because of liberalized liver donor selection criteria, all potential donors should be discussed with the local OPO before making any decisions about donor suitability.
2. Livers with a macrovesicular steatosis more than 30% should be approached with caution, weighing the risks and benefits for the intended recipients.
3. Most other factors by themselves do not contraindicate liver transplantation. The critical care physician should be aware of these issues, but successful transplantation has been routinely completed with these "marginal" organs.

Should Hypernatremia Be Avoided in Liver Donors? Maintenance of a normal serum sodium level in the potential organ donor is the most extensively studied strategy aimed at optimization of liver allograft function. Hypernatremia at organ procurement has been demonstrated to be an independent risk factor for early graft failure (142, 143). Organs removed from donors with serum sodium levels more than 155 mEq/L have been reported to have an increased need for retransplantation at 30 days (144). Furthermore, the risk of allograft failure at 90 days may be two or three times greater in livers from hypernatremic donors compared with organs from donors with normal serum sodium levels. The purported adverse effects of hypernatremia on liver graft function have been challenged by other studies (141, 280, 281). Limited evidence supports the theory that reversal of hypernatremia before organ procurement may improve early allograft function. In one study, livers from hypernatremic donors had a 90-day failure rate of 33%, whereas those from donors with normal serum sodium levels had a 90-day failure rate of 12.7%. Organs from donors who were initially hypernatremic but underwent correction of their serum sodium to less than 155 mEq/L before liver retrieval had a 90-day failure rate of 11% (282), but this hypothesis has never been formally evaluated with a prospective, controlled trial.

Recommendation:

1. Pending further definitive studies, hypernatremia in the potential organ donor should be corrected as a way of optimizing hepatic allograft function. At a minimum, the sodium level should be less than 155 mEq/L. It is not known if further correction leads to improved outcomes.

What Is the Optimum Hemodynamic Management in the Potential Liver Donor Patient? Hemodynamic compromise often is the result of severe cerebral edema or brain death. Donor hypotension has been associated with reduced liver allograft function and increased recipient length of stay in retrospective analyses (283–285), so the mean arterial blood pressure should be kept at or above 60–70 mm Hg (286). Pressors are commonly used in potential organ donors. In a series of high-risk liver donors, the 90-day hepatic graft survival was similar in donors who required more than 10 μg/kg/min of dopamine and those who received smaller doses (287).

Recommendations:

1. The hemodynamic status of potential liver donors should be optimized.
2. The target blood pressure in the liver donor has not been defined by previous studies, but expert opinion suggests that the mean arterial pressure should be kept above 60–70 mm Hg.
3. The use of vasopressors in the liver donor does not reduce the ability of transplant surgeons to use the organ.

What Is the Optimum Nutritional Management of the Potential Liver Donor? Glycogen provides the body's primary depot of glucose and is primarily stored in the liver. Hepatic glycogen may provide nutrients during times of ischemia after organ recovery but before transplantation (288). Accordingly, it has been suggested that maneuvers to increase glycogen stores in a potential organ donor may optimize allograft function (286). Although this is a rationale for continuing nutritional support, studies examining the effect of this intervention on liver graft function have not been performed.

Recommendation:

1. In the absence of contraindications, nutritional support of the donor should be continued.

Is Bedside Ultrasound Useful in the Evaluation of the Potential Liver Donor? Bedside ultrasound has been suggested as a screening modality for the suitability of liver donation (289, 290). In the evaluation of hepatic steatosis and other liver abnormalities, bedside ultrasound has with a high sensitivity (96%) but a marginal specificity (68%).

Recommendations:

1. Ultrasound is not a routine screening modality in potential liver donors.
2. Bedside ultrasound plays a limited role in guiding percutaneous biopsy when histologic results are needed to determine suitability of the organ.

Is Infection a Contraindication to Liver Donation? Infection in organ donors is not a contraindication to liver transplantation

(291, 292). Multiple retrospective studies have demonstrated the safety of transplanting livers that were procured from donors with bacterial infections (96). Organs have been successfully transplanted from donors with Gram-positive endocarditis and bacteremia with no effect on 1-year survival (293, 294). Liver transplantation has also been successful utilizing grafts from donors with active meningitis (105). Additionally, those with hepatitis C can still be considered potential donors (295, 296); these organs are typically used in hepatitis C-infected recipients. Deceased donors with antibodies against hepatitis B core antigen can be considered for transplant, even into recipients with no HBV infection. Long-term antiviral therapy in the recipient of a hepatitis B core antibody-positive liver has successfully prevented hepatitis infection posttransplant (297).

Recommendations:

1. Livers can be procured from donors with active bacterial infections if they are receiving appropriate antimicrobial therapy.
2. Liver donors may be positive for hepatitis C or hepatitis B core antibody.

Lung Donors

What Criteria Should Be Used to Determine Whether Lungs Are Suitable for Donation? Ideal lung donor criteria are listed in **Table 7**. The majority of potential organ donors fail to meet these criteria, historically leading to lung recovery rates of only 15–25%. However, multiple studies suggest that use of more liberal "extended donor" criteria—older age, more extensive smoking history, and mild or focal chest radiographic abnormalities—results in recipient outcomes similar to those achieved with use of standard criteria (298).

Recommendation:

1. Ideal lung donation criteria are overly restrictive. Because many transplant programs now utilize more liberal criteria, all potential donors should be discussed with the OPO and lung transplant teams to determine suitability for lung donation.

What Is the Acceptable Lower Limit of Oxygenation to Permit Lung Donation? What Interventions Can Improve Oxygenation? Standard criteria for lung donation stipulate that suitable donors must have a Pao_2/Fio_2 ratio more than 300 mm Hg (i.e., Pao_2 > 300 mm Hg with 100% Fio_2 and 5-cm positive end-expiratory pressure [PEEP]). Although most centers abide by this threshold in selecting donors, there has been limited but conflicting experience with donors who deviate from this standard. In a retrospective review of transplants performed between 1988 and 1998 in France, donor Pao_2/Fio_2 less than 350 mm Hg was associated with a steep increase in the risk of death (299). In contrast, Luckraz et al (300) retrospectively reviewed 362 donor and recipient pairs over a 17-year period and found no difference in 1- and 5-year survival for recipients with donor Pao_2/Fio_2 less than 300 mm Hg compared with more than 300 mm Hg. Reyes et al (301) analyzed the UNOS database containing over 10,000 primary transplants in the United States and found that donor Pao_2/Fio_2 was less than 300 mm Hg in 18% of cases (n = 1,751 recipients); survival to 7 years for this group was similar to that of recipients in which donor Pao_2/Fio_2 exceeded 300 mm Hg. Notably, some transplant surgeons consider the gold standard for assessing oxygenation to be a sample obtained from the pulmonary veins after eliminating areas of atelectasis in the operating room with the chest open, but this has not been systematically studied.

TABLE 7. Ideal Lung Donor Criteria[a]

Age < 55 yr
Smoking history < 20 pack-years
Clear chest radiograph
Pao_2 > 300 mm Hg with 100% Fio_2 and positive end-expiratory pressure of 5 cm H_2O
Absence of significant chest trauma
No evidence of aspiration or sepsis
No prior cardiothoracic surgery
No organisms on donor Gram stain
No purulent secretions or gastric contents on bronchoscopy
No history of significant chronic lung disease

[a]Because many transplant programs now utilize more liberal criteria, all potential donors should be discussed with the organ procurement organization and lung transplant teams to determine suitability for lung donation.

Tailored lung donor management protocols involving diuresis, therapeutic bronchoscopy, chest physiotherapy, and lung recruitment maneuvers have been shown to improve oxygenation variables in donors who initially fail to meet the standard oxygenation requirement. In a study from Australia, an aggressive lung donor protocol led to achievement of a Pao_2/Fio_2 more than 300 mm Hg in 20 of 59 potential donors whose initial oxygenation fell below this threshold (302). A similar strategy, including use of a recruitment maneuver of pressure-controlled ventilation at an inspiratory pressure of 25 cm H_2O and PEEP of 15 cm H_2O for 2 hours, was utilized by the San Antonio Lung Transplant Program. Of 98 donors, one third converted from unacceptable to acceptable Pao_2/Fio_2 ratios in response to this protocol (303).

Another salvage technique is ex vivo lung perfusion. Lungs are recovered and the trachea intubated to permit mechanical ventilation. Simultaneously, the lungs are perfused with a hyperoncotic acellular perfusate that draws fluid out of the extravascular compartment. Over the course of 4–6 hours, edematous lungs are effectively dehydrated, leading to improvement in oxygenation. In the largest study to date, Cypel et al (304) from the Toronto Lung Transplant Program subjected 23 donor lungs to 4 hours of ex vivo perfusion. The Pao_2/Fio_2 ratio increased from a median of 335–443 mm Hg at 4 hours, and 20 of the 23 lungs were successfully transplanted, with short-term outcomes similar to those of conventionally selected lungs. Ex vivo perfusion is undergoing clinical testing and is not available at all transplant centers.

Recommendations:

1. A Pao_2/Fio_2 ratio more than 300 mm Hg is widely considered the minimum acceptable oxygenation threshold for lung donation. However, potential lung donors who fail to meet this criterion should still be discussed with the OPO representative, as maneuvers can be performed to improve oxygenation in some cases (see points 2 and 3 below) and some transplant centers will accept donors whose oxygenation falls below this threshold.
2. Donors who fail to meet this oxygenation threshold on initial assessment at the bedside should undergo a lung donor management protocol that aims to achieve a euvolemic state through judicious fluid administration with or without diuresis and also employs chest physiotherapy, therapeutic bronchoscopy, and recruitment maneuvers.
3. At some transplant centers as part of an investigative protocol, lungs that fail to meet the oxygenation threshold despite these steps still can be recovered and subjected to ex vivo perfusion, with the expectation that many of these organs will ultimately prove to be acceptable for transplantation.

Are There Specific Mechanical Ventilator Settings That Should Be Used to Support Potential Lung Donors? Historically, donor management protocols employed by OPOs recommended the use of tidal volumes in the range of 10–15 mL/kg when ventilating potential lung donors. However, as in other critical care situations, there is currently a trend to employ lower tidal volumes, higher PEEP, and pressure controlled or limited ventilator management to avoid ventilator-associated lung injury. A recent European multicenter randomized trial examined a lung protective ventilatory strategy similar to that used in patients with acute respiratory distress syndrome (ARDS) (305). Potential donors were randomized to one of two ventilatory strategies: a conventional protocol using tidal volumes of 10–12 mL/kg, 3–5 cm PEEP, and an open circuit for both suctioning and apnea tests; or a lung-protective protocol using tidal volumes of 6–8 mL/kg, 8–10 cm PEEP, a closed circuit for suctioning, continuous positive airway pressure equal to previous PEEP for apnea tests, and recruitment maneuvers after any disconnection from the ventilator. Use of the lung-protective protocol doubled lung recovery rates (54% vs 27%; $p < 0.005$) compared with the conventional ventilator protocol.

A smaller, single-center retrospective study of 45 potential lung donors compared lung transplantation rates when a standard, assist-control ventilatory mode was used versus when airway pressure release ventilation was used (306). Donors managed with the latter had a significantly higher rate of successful lung recovery (84% vs 18%) and similar graft survival rates when compared to the conventionally ventilated group and to national averages.

Recommendation:

1. Ventilator strategies utilizing low stretch protocols and measures to recruit atelectatic lung appear to enhance recovery rates and should be strongly considered.

Should Bronchoscopy Be Performed on All Potential Lung Donors? Bronchoscopy allows an easy and quick visual assessment of the airway anatomy and has been shown to add to noninvasive assessments. Riou et al (307) reported that bronchoscopy was abnormal in 10 of 26 potential organ donors (38%) with normal radiographs and Pao_2 more than 400 mm Hg. The most common bronchoscopic abnormalities included aspirated gastric contents or blood and purulent secretions (307), the presence of which are a relative contraindication to lung donation if not cleared with suctioning.

Bronchoscopy can also clear mucous plugs or blood clots that may contribute to impaired oxygenation. Gabbay et al (302) incorporated bronchoscopic airway clearance measures into a lung donor management protocol that resulted in significant improvement in oxygenation and use of donors who would not otherwise have been deemed acceptable. Because the protocol included other interventions (antibiotics, fluid management, and ventilator adjustments), it is impossible to determine the role that bronchoscopy played in the observed improvements.

Recommendation:

1. Bronchoscopy should be performed in all potential lung donors, both to assess for occult aspiration and infection and to perform therapeutic airway clearance.

Is There a Specific Fluid Management Strategy That Is Optimal for Lung Donation? Limited data exist on lung procurement and recipient outcomes with regard to different fluid management protocols, but studies in patients with ARDS may provide some insight. One large prospective trial randomized patients with ARDS to either a liberal fluid management strategy (target CVP, 10–14 mm Hg or PAOP, 14–18 mm Hg) or a conservative strategy (target CVP, < 4 mm Hg and PAOP, < 8 mm Hg) (308). The conservative fluid strategy was associated with superior oxygenation and a decrease in duration of mechanical ventilation and need for intensive care, as well as no increase in nonpulmonary organ failure (e.g., renal and hepatic).

The best evidence supporting a conservative fluid management strategy in potential lung donors comes from the San Antonio Lung Transplant group. As part of a lung donor-specific management protocol, they incorporated a fluid management strategy that minimized use of crystalloids and employed diuretics to maintain neutral or negative fluid balance (303). Their protocol was associated with increased lung procurement without affecting other organs for transplantation, but the degree to which this was due to conservative fluid management as opposed to other components of their protocol (e.g., recruitment maneuvers) cannot be determined. Results of a study of 404 kidney recipients provide assurance that a conservative fluid strategy with CVP below 6 mm Hg does not adversely affect renal graft survival or increase the risk of delayed graft function (118). This argues against the widely held notion that fluid strategies to optimize lung and kidney donation are in direct conflict.

Recommendation:

1. Fluid management protocols, aiming for neutral or net negative fluid balance to avoid volume overload and maintenance of blood pressure with vasopressors rather than

aggressive fluid resuscitation, are recommended to optimize lung procurement.

Pancreas Donors

What Is Optimal Fluid Management for the Pancreas Donor? Although an optimal CVP for the pancreas is unknown, aggressive fluid resuscitation with crystalloid may result in an edematous pancreas, which is frequently rejected for transplantation. A CVP considered optimal for both thoracic organs and kidneys is likely reasonable for the pancreas as well. No literature support is found for preferential use of colloid versus crystalloid during organ procurement, but most pancreas transplant surgeons favor colloid resuscitation to minimize edema at cross-clamping. The pancreas has a higher prevalence of graft thrombosis related to the relatively low-flow state, so an edematous pancreas should be avoided, as the increase in intraparenchymal pressure from the edema could exacerbate clotting.

Recommendation:

1. To avoid development of pancreatic edema that would render the organ unsuitable for transplantation, maintenance of a euvolemic state in the donor is recommended as a general guideline for fluid resuscitation.

Do Data Support the Use of Hormone Replacement to Optimize Function and Utilization of the Deceased Donor Pancreas? DI occurs in most deceased donors as a result of the loss of the pituitary-hypothalamic axis (309), resulting in severe hypernatremia, hypocalcemia, hypokalemia, and hypomagnesemia. Because hypernatremia may be associated with primary nonfunction of the liver (142, 143), these donors are treated with free water and desmopressin. Two brief reports suggest a higher risk of pancreas graft thrombosis if the organ came from a desmopressin-treated donor (153, 154), but this agent is used extensively in deceased donors and no other reports have reported such findings.

Although specific improvement in the overall function of the pancreatic allografts was not reported, a marked increase in organ utilization was associated with hormone replacement (165, 310).

Recommendation:

1. Use of HRT should be considered to optimize donor pancreas utilization.

Is Control of Hyperglycemia Beneficial to the Pancreas Donor? Deceased donors frequently suffer from marked hyperglycemia, in part due to insulin resistance and steroid administration. Significant hyperglycemia (> 200 mg/dL) has been found in a large proportion of deceased donors and was associated with decreasing renal function at organ recovery (157). Donor hyperglycemia was a risk factor for pancreas allograft loss in a case series reported from the University of Minnesota (192). Maintenance of reasonable blood glucose levels (< 180 mg/dL) is increasingly seen as a standard of care in deceased donors. As a result, many deceased organ donors likely will receive continuous IV insulin. If the pancreas donors have no history of diabetes or insulin requirements, the preprocurement insulin requirements should have no bearing on outcome or recovery.

Recommendations:

1. Preprocurement insulin requirements should have no bearing on decisions to utilize the pancreas.
2. Maintenance of donor blood glucose levels less than 180 mg/dL is recommended to optimize deceased organ donor management.

Small Bowel Donors

Few studies have evaluated the effect of variation in donor treatment strategies on the quality or subsequent function of the small bowel allograft. Although many OPOs have protocols for insulin administration, thyroxine therapy, and IV antibiotic prophylaxis, such protocols have not been evaluated in the small bowel donor.

How Are Donors Selected for Small Bowel Transplantation? The selection of small bowel donors varies somewhat from donor selection for other organ allografts. The unique consequences of intestinal ischemic injury could result in bacterial translocation or intestinal perforation, so donors with excessive vasopressor requirements or prolonged arrest and donation after circulatory death are generally avoided (311–313). Matsumoto et al (311), however, demonstrated adequate function without apparent untoward effects in intestinal allograft donors who had up to 20 minutes of cardiopulmonary resuscitation when the terminal transaminases had returned to normal. One of the largest differences between small bowel donors and other solid-organ donors is the intentional use of those who are considerably smaller than the intended recipient, due to the "loss of domain" (i.e., constriction in the peritoneal cavity after removal of native intestine segments) experienced by recipients with short bowel syndrome.

Recommendations:

1. Aggressive resuscitation of the potential small bowel donor, especially after hypotension or cardiopulmonary arrest, is warranted to return organ function to normal or near-normal levels prior to organ procurement.
2. Donors with excessive vasopressor requirements, prolonged arrest, or circulatory death are generally avoided.
3. Small bowel donors should generally be considerably smaller than the intended recipient.

Should Donors Be Fed Enterally Before Organ Procurement? No uniform policy for donor feeding or fasting is practiced in the United States. A fairly common approach appears to be fasting initiated at the declaration of brain death. Decreased mucosal integrity and villus height have been found in animals fasting for 12 hours before procurement compared with fed animals (314), but this has not been studied in humans.

Recommendation:

1. Given the generally perceived protective effects of enteral feedings on mucosal structure, continuation of tube feedings should be considered in the potential small bowel donor after pronouncement of brain death.

Should Antibiotics Be Administered to Small Bowel Donors? IV administration of antibiotics is essentially universal for small bowel donors. Although variations in OPO protocols exist, most utilize broad-spectrum prophylaxis and tailor coverage to expected organisms for donors with fever or elevation of the WBC count once specific organisms are identified in cultures. Protocols for the initiation of antibiotics in the afebrile organ donor vary: some start early after declaration of brain death, others delaying administration until 12–24 hours before organ recovery.

Intestinal decontamination with enteral antibiotic mixtures is aimed at decreasing the bacterial content of the intestinal allograft. Enteral administration of antibiotics is not standard in most other solid-organ procurements; it is limited primarily to donors of small bowel grafts and some who donate the pancreas with an attached segment of duodenum. Specific enteral decontamination practices used by individual centers vary considerably, and the therapy has not been rigorously studied in humans. An early experience reported by the University of Nebraska utilized a combination of oral antibiotics and a polyethylene glycol electrolyte lavage solution (315). Later reports from this center suggested that cessation of enteral antibacterials had no apparent untoward effect in the recipient (316). In contrast, the University of Pittsburgh program utilizes enteral administration of amphotericin and neomycin in all small bowel donors (G Mazariegos, personal communication, 2010). In light of animal studies suggesting increased injury to the small bowel mucosa with enteral decontamination regimens using povidone-iodine, this agent should not be used (317).

Recommendations:

1. The ICU team should consult with the OPO coordinator early after declaration of brain death to determine if small bowel donation is likely, and if so, whether the receiving center utilizes a small bowel decontamination regimen.
2. Local OPO protocols should be followed on administration of IV broad-spectrum bacterial prophylaxis prior to organ procurement.
3. Because animal studies suggest it causes increased mucosal injury, avoid povidone-iodine as a component of a small bowel decontamination regimen.

Is Gastrointestinal Bleeding or Heme-Positive Stool a Contraindication to Small Bowel Donation? No organ-specific human studies address this question. Frank blood or heme-positive stools could be an indication of severe mucosal injury and ulceration and raise concern for utilization of the small bowel allograft.

Recommendation:

1. The ICU team should alert the OPO coordinator of the presence of gastrointestinal bleeding or heme-positive stool as it could be a contraindication to small bowel donation.

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APPENDIX 1: DONOR MANAGEMENT TASK FORCE

Task Force Chairs

Robert M. Kotloff, Sandralee Blosser, Gerard J. Fulda

Subcommittee Chairs

Donation After Circulatory Determination of Death: Gerard J. Fulda
Death Determination Using Neurologic Criteria: Michael A. DeVita, Thomas E. Grissom
Authorization Process: Scott D. Halpern
General Contraindications to Organ Donation: Malignancy and Infection: Robert M. Kotloff
Hemodynamic Management: Kenneth Wood
Endocrine Dysfunction and HRT: Vivek N. Ahya
Pediatric Donor Management Issues: Thomas A. Nakagawa
Cardiac Donors: Sandralee Blosser
Kidney Donors: Darren Malinoski
Liver Donors: Matthew C. Byrnes
Lung Donors: Luis Angel
Pancreas Donors: Peter G. Stock
Small Bowel Donors: Debra L. Sudan

Committee Members

Sergio J. Anillo, Selim Arcasoy, Thomas P. Bleck, Jerry Eichner, Cynthia Gries, Dan Herr, Akhtar Khan, David Landsberg, Deborah Jo Levine, Mudit Mathur, Priyumvada Naik, Claus U. Niemann, David R. Nunley, Shawn J. Pelletier, Omar Rahman, Ali Salim, Robert G. Sawyer, David Sonneti, Peter Spiro, Maryam Valapour, Deepak Vikraman-Sushama, Timothy P. M. Whelan, Zarinne Balsara, Ted Barnett, Michael Porter, Dinesh Ranjan, Steven E. Ross, Tasnim Sinuff, Betsy Tuttle-Newhall, Brian Untch

Association of Organ Procurement Organizations Expert Advisors

Elling Eidbo, Rick Hasz, Rick Fowler, Dan Lebovitz, Kevin O'Connor