Management of the Pediatric Organ Donor

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Management of the pediatric organ donor necessitates understanding the physiologic changes that occur preceding and after death determination. Recognizing these changes allows application of the therapeutic strategies designed to optimize hemodynamics and metabolic state to allow for preservation of end-organ function for maximal organ recovery and minimal damage to the donor grafts. The pediatric pharmacist serves as the medication expert and may collaborate with the organ procurement organizations for provision of pharmacologic hemodynamic support, hormone replacement therapy, antimicrobials, and nutrition for the pediatric organ donor.

ABBREVIATIONS ACCP, American College of Chest Physicians; ADH, antidiuretic hormone; APO, Association of Organ Procurement Organizations; CVP, central venous pressure; D5W, dextrose 5% in water; DI, diabetes insipidus; DCDD, donation after circulatory determination of death; DNDD, donation after neurological determination of death; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; OPTN, Organ Procurement and Transplantation Network; OPO, organ procurement organization; T3, triiodothyronine; T4, tetraiodothyronine

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Pediatric Deceased Organ Donation

Organ grafts may be recovered from a deceased organ donor, with pediatric donors accounting for approximately 8% of the grafts since 1988 (based on Organ Procurement and Transplantation Network [OPTN] data as of May 20, 2018). The deceased donor pathway may be satisfied through donation after neurologic determination of death (DNDD) or donation after circulatory determination of death (DCDD). More than 70% of all pediatric donors satisfy death by neurologic criteria; however, there has been a growing trend in pediatric DCDD during the past decade: Rates increased from under 2% of all deceased pediatric donations prior to 2000 to 15% of all pediatric deceased donations in the past 5 years (based on OPTN data as of May 20, 2018).

DNDD is brain death, which is defined as the irreversible cessation of whole-brain function. The DNDD patients are often referred to as “beating-heart donors” because the patient’s heart continues to beat, although cerebral function is absent. In order to determine brain death, the patient should be assessed in the presence of normal physiologic parameters. The rationale for this is to eliminate any potential factors that may influence or suppress brain function, such as hypotension, hypothermia, and metabolic disturbances. Sedatives, analgesics, neuromuscular blockers, and anticonvulsant agents should be discontinued to ensure they do not affect the neurologic exam. The desired time interval for drug washout prior to the neurologic exam is dependent on the elimination half-life of the drug. Once deemed appropriate to proceed with the brain death evaluation,

the patient will undergo clinical assessment of his or her comatose state, brainstem reflexes (i.e., pupillary, corneal, oculo-cephalic, oculo-vestibular, cough, and gag reflex), and respiratory drive. Comatose state must be present with the absence of all brainstem reflexes and respiratory drive in order to declare brain death.^{1,2}

In order to declare brain death in a child, 2 clinical exams must occur. The time interval between those exams is dependent on the patient’s age, institution policy, and the state law. Typically, neonates must have 24 hours separating the clinical exams, whereas children older than a month may have the second clinical exam after 12 hours. Ancillary tests, such as electroencephalogram and the radionuclide cerebral blood flow scan, are not required to establish brain death, and they are not substitutes for the neurologic clinical exam. The national guidelines recommend using these tests to supplement the clinical exam if any of the components cannot be performed safely.^{1,2}

Cardiac death, which is the characteristic classification of death, is the cessation of cardiac function and respiratory effort. Pediatric cardiac death determination includes a clinical exam to confirm immobility, apnea, and absence of arterial pulsatility with an observation period of 2 to 5 minutes required for DCDD. Successful organ recovery after DCDD is dependent on the time of warm ischemia. Warm ischemia is the time the organ remains in a normothermic environment but is exposed to diminished or absent perfusion with resultant ischemic injury. In the DCDD patient, warm ischemia time is the time from asystole to time of cold

perfusion during organ procurement.³ For controlled DCDD, organ recovery may proceed if death occurs within 60 minutes. If the determination of cardiac death cannot be made in less than 60 minutes, then the patient resumes end-of-life care. Uncontrolled DCDD may also occur in the event of sudden death; however, this may complicate successful organ recovery but still allows tissue donation.

Pathophysiology of Brain Death

A number of deleterious changes transpire after brain death that may endanger the viability of organ grafts. Brain death is the result of cerebral herniation through the foramen magnum, often due to elevated intracranial pressure or space-occupying intracranial lesions (e.g., hematoma, tumors), leading to brainstem ischemia.^{4–6} Proceeding cerebral ischemic injury manifests in a number of systemic failures.

In the superior portion of the brainstem, pontine ischemia results in parasympathetic and sympathetic activation that manifests in the Cushing triad (bradycardia, hypertension, and irregular breathing).^{4,5} As the ischemia descends the brainstem, the parasympathetic-innervated structures of the medulla are damaged, leaving the sympathetic stimulation unopposed.⁵ This is often referred to as the “catecholamine surge” or “autonomic storm” observed in brain death. The surge of excess of dopamine, epinephrine, and norepinephrine manifests as vasoconstriction, hypertension, tachycardia, and increased myocardial oxygen demand, but this excess will be depleted over time, resulting in hypotension.⁵ Inferior brainstem ischemia involving the spinal cord results in vasodilation and subsequent hypotension from loss of vasomotor tone.^{4,5}

Neuroendocrine failure is present in brain death as perfusion ceases to the hypothalamic and pituitary structures.⁵ Hypothalamic failure manifests a thermoregulation leading to hypothermia most commonly in brain-dead patients. The compensatory mechanisms to increase core temperature through shivering or vasoconstriction are lost in this group. Adverse effects of hypothermia include arrhythmias, diuresis, coagulopathy, and insulin resistance. Ischemia of pituitary gland impairs hormone secretion, thus decreasing circulating levels of adrenocorticotrophic hormone, antidiuretic hormone (ADH), and thyroid-stimulating hormone. Deficiency in adrenocorticotrophic hormone has been reported and may impair donor stress response.⁷

Diabetes insipidus (DI) originating from ADH depletion results in free water loss, hypovolemia, and hypernatremia.⁵ Decline in circulating free triiodothyronine (T3), reduced peripheral conversion of tetraiodothyronine (T4), and absence of thyroid-stimulating hormone secretion results in functional hypothyroidism.^{5,8} This is particularly detrimental to the donor heart, because reductions in T3 result in decreased cardiac contractility, depletion of intracellular energy stores, increased

anaerobic metabolism, and subsequent lactate accumulation.^{5,8}

Hyperglycemia is common with brain death and is likely multifactorial. Hyperglycemia may be due to insulin level decline and enhanced gluconeogenesis after brain death, as well as exogenous influences with catecholamine administration, infusion of dextrose-containing fluids, and corticosteroid administration. Additionally, peripheral insulin resistance, altered intracellular metabolism, and hypothermia seen in brain death may contribute to hyperglycemia.⁹ An inflammatory response is mounted secondary to ischemic injury, catecholamine surge, and metabolic derangement seen in brain death.⁶ This proinflammatory state may provoke disseminated intravascular coagulation (DIC) and platelet dysfunction, which may precipitate donor graft damage.⁶

Not all physiologic changes are seen in every donor with brain death; however, the likelihood of these adverse effects increases with time after onset of brainstem ischemia.⁹ Hypotension and DI are most commonly encountered in pediatric brain-dead organ donors followed by anemia and hyperglycemia.¹⁰ Hypotension is greatly concerning because it compromises end-organ perfusion of the potential grafts, thus endangering organ viability. Diabetes insipidus may contribute to dehydration, which in turn may exacerbate hypotension. Anemia threatens hypoxic injury to the potential grafts, whereas hyperglycemia may potentiate pancreas allograft loss.¹¹ Therefore, it is no surprise that donor management in a child is targeted towards mitigating these adverse physiologic changes.

Goals of Pediatric Donor Management

The goals of organ donor management include the maintenance of the optimal hemodynamics and metabolic state, preservation or improvement of end-organ function in order to maximize organ recovery and minimize the damage to the donor graft. Increasing organ viability can be accomplished by normalizing hemodynamics, acid-base balance, electrolytes, body temperature, and lung mechanics, which requires intensive care unit (ICU)-level monitoring and intervention.

For hemodynamic optimization, the pediatric donor blood pressure should be normalized for age (above fifth percentile). To optimize fluid balance, central venous pressure (CVP) should be maintained at 5 to 8 mm Hg (acceptable up to 11 mm Hg) and urine output between 1 to 4 mL/kg/hr. Serum pH above 7.30 and below 7.45 should be achieved. Electrolytes and serum glucose should be kept within the normal range. Normothermia should be targeted above 35°C and below 37.5°C. The ventilator should be adjusted to optimize oxygenation and ventilation with an oxygen saturation above 95% and partial pressure of oxygen above 100 mm Hg.^{12,13}

Due to the nature of illness and injury that precedes

DNDD as well as the monitoring and interventions necessary after declaration of brain death, these children will receive ICU-level care. The management of the deceased organ donor is dictated by the Organ Procurement and Transplantation Network (OPTN) via their surrogates, the regional organ procurement organizations (OPO). The OPOs have the duty to manage and document achievement of these goals and transmit these findings to the receiving OPOs or transplant hospitals, whereas the ICU staff provide the bedside interventions (e.g., medication administration, ventilator management, etc.) under the direction of the OPO.¹⁴ Unfortunately, the evidence basis for pediatric donor management is lacking, but logically applying physiologic-based critical care management and extrapolating the evidence from adult donor management is the strategy recommended by the Association of Organ Procurement Organizations (AOPO).¹²

Pediatric Pharmacist Role in Donor Management

Although there is no literature to describe the pediatric pharmacist impact in pediatric organ donor management, the provision of direct patient care should not change from pre-mortem to post-mortem for donor patients. The pediatric pharmacist is obliged to provide safe and effective medication management and to monitor for toxicities through organ recovery. The pharmacist's knowledge of drugs and the medication use process is helpful to inform the protocols and procedures of the OPOs, because many of the OPO personnel are not former pediatric practitioners or attuned to the special drug therapy needs of critically ill children. The pediatric pharmacist can help in product selection based on formulary and inventory, assist in cost containment decisions, and engage in antimicrobial stewardship activities with the OPO to align with institutional practices. It is also important to collaborate with the OPO team in the creation of medication use guidelines and clinical decision support tools to assist with the appropriate prescribing of these medications (Table 1).

Pharmacologic Donor Management in Children

Hemodynamics. The principles for hemodynamic management of the pediatric organ donor do not differ greatly from those for a critically ill child. The goal remains to optimize cardiac output to ensure end-organ perfusion with the end point of preserving donor graft viability.

Cardiac output is a function of heart rate and stroke volume, and stroke volume is affected by cardiac contractility, preload, and afterload, all of which can be augmented with medications. Intravenous fluids, diuretics, antihypertensives, and vasoactive infusions

provide the medication arsenal to manage hemodynamics in pediatric organ donors.

Hypovolemia frequently occurs in DNDD patients and is likely the result of cold diuresis from hypothermia, third-spacing from the inflammatory process, osmotic diuresis from hyperglycemia or hyperosmotic agent administration, and DI from neuroendocrine failure, thus contributing to low preload in these patients.⁹ In a low preload state, intravenous crystalloid fluids are recommended for fluid resuscitation in pediatric organ donors. The risk of hyponatremia with administration of hypotonic intravenous maintenance fluids to hospitalized children has been well documented in a number of publications.^{15–18} Therefore, the recommendation is to use isotonic crystalloid fluids in pediatric donors.¹³ Colloid products, specifically blood products, may be necessary to treat underlying anemia and coagulopathy as well as increase intravascular volume.

The goal is to achieve euvolemia, maintain end-organ perfusion, normalize serum lactate, and achieve a CVP of less than 8 mm Hg.¹² The impression that hypovolemia may harm the kidney graft and hypervolemia may be deleterious to the lung graft (e.g., neurogenic pulmonary edema) are competing interests for maintenance of fluid balance in the organ donor. In a study of 26 adult donors, pulmonary gas exchange was optimized at CVP of 4 to 6 mm Hg and found to be compromised with a CVP of 8 to 10 mm Hg.¹⁹ A similar investigation of adult donors reported increased heart and lung procurement when a CVP of less than 10 mm Hg was achieved with concurrent hormonal replacement therapy.²⁰ Restrictive fluid management (negative or equal fluid balance with CVP under 6 mm Hg) has not been found to be harmful for kidney graft survival or development of delayed kidney graft function, suggesting the recommended donor resuscitation goals preserve multiorgan donor perfusion.²¹ In a high preload state with elevated CVP (e.g., fluid overload), diuretics may be useful to remove excess fluid, but this must be done cautiously to avoid compromising end-organ perfusion.

High vascular tone and hypertension attributed to a catecholamine surge is infrequent and often limited to the early stages of brain injury before declaration of brain death or shortly thereafter. Short-acting intravenous agents, such as esmolol, nicardipine, and nitroprusside, are desired antihypertensives to help eliminate injury to organ grafts.^{22,23} Esmolol is an effective quick-acting antihypertensive that may be considered to treat catecholamine-induced hypertension. Nicardipine and nitroprusside are antihypertensive agents with peripheral vasodilating properties. Both agents have quick onset and relatively short half-lives, which is important in the DNDD patient, who may quickly transition from the catecholamine surge to the catecholamine deplete phase. A small retrospective study described the effect of catecholamine surge on the potential heart graft of 46 brain-dead adult patients.²⁴ Of the 63% of po-

Table 1. Pediatric Organ Donor Medication Recommendations

Donor Issue and Medication*	Dose Recommendation ⁸²
Hormonal replacement	
Methylprednisolone	20–30 mg/kg
Levothyroxine ⁷⁰	
Birth–6 mo	5 mcg/kg bolus followed by 1.4 mcg/kg/hr
6–12 mo	3 mcg/kg bolus followed by 1.2 mcg/kg/hr
1–5 yr	1.5 mcg/kg bolus followed by 0.8 mcg/kg/hr
6–12 yr	0.8 mcg/kg bolus followed by 0.8 mcg/kg/hr
Above 16 yr	0.05–0.2 mcg/kg/hr
Liothyronine	0.05–0.2 mcg/kg/hr
Diabetes insipidus	
Vasopressin	0.5 milliunits/kg/hr, titrate to UOP 3–4 mL/kg/hr
Desmopressin	0.5 mcg/hr, titrate to UOP 3–4 mL/kg/hr
Hemodynamically unstable	
Volume replacement (isotonic crystalloids, 5% albumin)	20 mL/kg IV bolus
Inotropic support	
Dobutamine	2–20 mcg/kg/min
Dopamine	2–20 mcg/kg/min
Epinephrine	0.01–1 mcg/kg/min
Milrinone	0.25–0.75 mcg/kg/min
Vasopressor support	
Norepinephrine	0.01–1 mcg/kg/min
Phenylephrine	0.1–0.5 mcg/kg/min
Vasopressin [†]	0.0003–0.002 unit/kg/min
Antihypertensive	
Esmolol	100–500 mcg/kg followed by 50–250 mcg/kg/min
Nicardipine	1–5 mcg/kg/min
Nitroprusside	0.5–10 mcg/kg/min
Metabolic acidosis	
Sodium bicarbonate	1 mEq/kg
Hyperglycemia	
Insulin	0.05–0.1 unit/kg/hr, titrate to serum glucose goal range

UOP, urine output

* All medications are given intravenously, unless otherwise specified.

† Note that dose and units are different from diabetes insipidus recommendations.

tential donors with hypertension due to catecholamine surge, 41% of the group received antihypertensives. This study found that the DNDD patients who received antihypertensives had improved left ventricular ejection fraction compared with the untreated group ($p = 0.049$). Additionally, the treated donors were 8.8 times more likely to have a successful cardiac graft procurement ($p = 0.002$).²⁴ Although this is small study, it does suggest that treatment of the catecholamine surge in DNDD patients may be of benefit.

Hypotension is very common in pediatric organ donors; unfortunately, there is no preferred vasoactive treatment option in donor patients. The drug choice is based on the individual patient's hemodynamics and the ability to preserve the donor grafts. Dopamine is traditionally considered as the first-line vasoactive agent in organ donors, which is consistent with the recommendation for an initial vasoactive infusion in pediatric shock.²⁵ Other agents with beta-1 agonism, such as dobutamine, epinephrine, and norepinephrine, may

be considered as well. However, beta-agonist therapy should be used with caution in potential heart donors, based on animal modeling that suggests myocardial cellular energy depletion and desensitization of beta-receptors at infusion rates higher than 10 mcg/kg/min dopamine or equivalent.^{23,26} Large-dose dopamine and epinephrine as well as norepinephrine exhibit alpha-agonist activation, leading to vasoconstriction. Excessive vasoconstriction may have detrimental effects on end-organ perfusion, especially in the coronary and mesenteric vasculature.^{13,23}

Milrinone is a phosphodiesterase-3 inhibitor that has positive inotropic effects as well as lusitropic effects, which enhance myocardial contraction and relaxation, respectively. However, the increase of cyclic adenosine monophosphate in the peripheral vascular smooth muscles may lead to systemic hypotension, thus compromising perfusion. Phenylephrine through alpha-agonism and vasopressin through vasopressin receptor stimulation both function as primary vasoconstrictors, which may not be desired because this may compromise end-organ perfusion. Vasopressin is an interesting choice because it serves dual purposes as cardiovascular support and hormonal replacement therapy in pediatric organ donors. One retrospective study hypothesized that low-dose vasopressin given to DNDD children would exert a pressor effect without major organ toxicity.²⁷ The vasopressin group was 7 times more likely to be weaned from alpha-agonists (norepinephrine and phenylephrine) than the control group (78% versus 0%, $p < 0.01$). No vasopressin-induced arrhythmias, hypertension, or anuria was described. No difference was detected in the donor graft function (kidney, liver, heart) between the 2 groups ($p > 0.05$). This study demonstrated the vasopressor-sparing effects of vasopressin in critically ill children with brain death.²⁷

The choice of vasoactive agent in the pediatric donor should take into consideration the status of the donor heart function and vascular tone. In primary cardiac dysfunction, dobutamine, dopamine, epinephrine, and milrinone are all reasonable options to enhance inotropy. In primary vasodilatory shock, norepinephrine, phenylephrine, and vasopressin are vasoconstrictors that can be considered. Combination therapy is also a reasonable approach, and great strategy to minimize the doses of individual agents.^{12,13,23} The consensus recommendation put forth by the Society of Critical Care Medicine, American College of Chest Physicians, and APOPO recommends aiming for the lowest dose of vasopressors with doses of dopamine under 10 mcg/kg/min or similar equivalent.¹³

Vasoactive drug effects on donor graft outcomes have been investigated in adult donors with reports of favorable graft outcomes. Donor dopamine use has been associated with provoking a faster drop in serum creatinine after transplantation, decreasing the need for

postoperative hemodialysis, reducing acute rejection, and improving graft survival in kidney recipients.^{28–30} However, in a recent publication, dopamine pretreatment has not been found to improve 5-year survival of kidney grafts.³¹ Norepinephrine use in the donor has been blamed for cardiac dysfunction, with doses of norepinephrine above 0.1 mcg/kg/min often leading to declination of donor heart grafts. However, a recent study challenged this practice by demonstrating no difference in immediate postoperative outcomes (graft dysfunction, prolonged ventilation, renal replacement therapy) or 30-day and 1-year mortality in heart grafts exposed to small-dose or large-dose (above 0.1 mcg/kg/min) norepinephrine.³² In kidney grafts, norepinephrine has also had favorable outcomes similar to dopamine, decreasing the risk of acute rejection and improving 4-year graft survival.²⁸

Acid-Base and Electrolytes. Achieving physiologic hemostasis is a prerequisite to proceed with neurologic determination of death, but it is also advantageous in the donor management phase to enhance donor stability and graft function. Acid-base balance should be maintained with an arterial pH between 7.30 and 7.45 to optimize enzymatic processes and membrane potentials.¹³ Sodium bicarbonate in intravenous fluids may be considered in donors with metabolic acidosis.¹³

Serum electrolytes and glucose should be preserved within normal ranges. Hyponatremia (sodium greater than 155 mEq/L) is quite common in the DNDD patient from fluid resuscitation, residual effects of hyperosmolar agents for intracranial hypertension treatment, and DI. Prolonged hyponatremia has been associated with negative outcomes in adult hepatic grafts, although pediatric liver transplantation data lack this association.^{33–36} During the donor management period, if non-DI-associated hyponatremia persists, hypotonic fluids should be considered to return the donor's serum sodium to the normal range. Hypotonic fluids, such as dextrose 5% in water (D5W), and 0.45% and 0.225% sodium chloride, are typically used to normalize the serum sodium. The risks with hypotonic fluid administration include cerebral edema and hemolysis. Cerebral edema from too rapid a decline in serum sodium is an unnecessary concern in a brain-dead patient. However, the risk of hemolysis-associated acute kidney injury from hypotonic fluid administration remains.^{37–39} Hypotonic fluids pose a hemolysis risk with increased contact time and volume of hypotonic fluid administered.^{40,41} D5W is a hypotonic fluid, but it is considered iso-osmolar (253 mOsmol/kg), whereas 0.45% and 0.225% sodium chloride are both hypotonic and hypo-osmolar.⁴² Thus, D5W would be a better choice for hyponatremia correction and avoidance of hemolysis potential; however, it would be undesirable in the hyperglycemic donor. No matter the inciting factor for hyponatremia, serum sodium concentration should be corrected to less than 155 mEq/L with an appropriate management strategy.¹³

Endocrine Abnormalities. Endocrine abnormalities are common in DNDD patients, and hormone replacement therapies uniquely address these issues. Manifestations of neuroendocrine failure include DI from ADH deficiency, hemodynamic instability from thyroid hormone depletion, and hyperglycemia from gluconeogenesis and insulin resistance.^{4,9} Hormone replacement therapy with insulin, corticosteroids, thyroid hormone, and vasopressin may help attenuate these manifestations.

Hyperglycemia (glucose above 180 mg/dL) is common after brain death, and is likely multifactorial due to massive catecholamine release or exogenous catecholamine administration, infusions of dextrose-containing fluids, corticosteroid administration, peripheral insulin resistance from catechol exposure, and altered intracellular metabolism.⁹ Hyperglycemia has been reported in up to 64% of brain-dead adult donors, 48% of pediatric donors younger than 5 years, and 28% of pediatric donors ages 5 to 12 years.^{10,43} Hyperglycemia above 200 mg/dL is associated with pancreatic beta cell injury and linked with pancreatic graft failure.¹¹ Higher glucose values and variability in serum glucose is associated with worse donor renal function, greater kidney recipient reperfusion injury, and delayed renal graft function.^{44,45}

There are a number of studies that support the use of insulin for treatment of hyperglycemia in critical illness; unfortunately, none of these include organ donors.^{46–50} A large report of DNDD patients revealed that insulin had little beneficial effect when used in combination with hormonal replacement therapies.⁵¹ However, the recommendation remains to manage hyperglycemia per institutional guidelines for critically ill children and aim for a serum glucose below 180 mg/dL.¹³ Permissive hyperglycemia during the short donor management window is likely not helpful, so managing serum glucose concentrations through an insulin infusion is advised.^{12,23}

Corticosteroids are commonly used in the critically ill for a variety of indications. Therefore, it is not surprising that corticosteroids have been introduced to organ donor management (Table 2). Methylprednisolone has been given in combination with cyclophosphamide to prevent and attenuate rejection episodes, but with mixed success.^{52–54} Similarly, hydrocortisone has been investigated to treat hemodynamic instability and alleviate vasopressor exposure, which has also had varied results.^{55–57} Large-dose methylprednisolone alone or in combination with other hormonal therapies has been the most studied corticosteroid in organ donors. Methylprednisolone is favored because of its potent glucocorticoid effects and short onset of action, and its administration appears to reduce the potential detrimental effects of the inflammatory cascade on donor organ function.⁵⁸ However, methylprednisolone has been shown to have neutral results when hemodynamics, oxygenation, organ recovery, graft survival, and patient survival were measured.⁵⁹ Corticosteroids are

unlikely to be detrimental to organ recovery and may have a greater benefit in donors who have not received thyroid products.⁵¹ The consensus recommendation supports administering large-dose corticosteroids early in the donor management phase, ideally after blood has been collected for tissue typing because corticosteroids have the potential to suppress human leukocyte antigen expression.^{13,23}

Exogenous supplementation of thyroid hormone is unique to organ donor management. The production of T3 and T4 declines after brain death and loss of the pituitary axis. Thyroid hormone depletion results in impaired cellular respiration through inhibition of the oxidative pathway for carbohydrates and fatty acids, shifting from aerobic to anaerobic metabolism and accumulating lactate.^{60,61} This cellular metabolic dysfunction has been implicated in loss of donor grafts, specifically cardiac grafts. Supplementation with thyroid hormone in the DNDD patient has been associated with improving cardiac allograft function and procurement.^{20,60,62–66} Similarly, donor hemodynamics have been improved and inotropic medication needs have declined with exogenous thyroid hormone administration.^{55,56,67–70} It is important to point out that the non-randomized studies have described beneficial effects with this therapy, whereas randomized controlled studies of thyroid hormone in donor management report neutral effects (Table 3). Nonetheless, the recommendation is for the donor is to receive thyroid replacement therapy if any of the following are present: myocardial dysfunction (left ventricular ejection fraction <45%), hemodynamic instability, and protracted donor management periods with likely need for substantial vasoactive support.^{13,71}

Two thyroid products are available for intravenous administration: liothyronine is the synthetic T3 product and levothyroxine is the synthetic T4 product. More studies have evaluated T3 administration rather than T4, although the one primary pediatric donor study investigated the effects of levothyroxine on vasopressor requirement on DNDD patients.⁷⁰ Levothyroxine requires hepatic biotransformation to the active moiety (T3), has higher protein binding and a prolonged half-life compared with T3. Aside from the pharmacokinetic differences, the discrepancy between the product cost favors levothyroxine because intravenous liothyronine is substantially more expensive than intravenous levothyroxine.

The final hormonal replacement therapy for neuroendocrine failure in the DNDD patient is ADH. Antidiuretic hormone is synthesized in the hypothalamus and released in vesicles by the posterior pituitary gland in response to hyperosmolarity, hypotension, and sympathetic stimulation. The role of ADH in the vasculature is as a potent vasoconstrictor, whereas in the kidney, ADH directs the nephrons to increase the amount of water reabsorbed back into the circulation. In brain death, ADH depletion manifests most commonly as DI,

Table 2. Studies of Corticosteroids in Donor Management*

Study	Pediatric Patients	Medication and Dose	Outcomes			
			Improve Hemodynamics	Improve Oxygenation	Organ Recovery	Graft Survival
Chatterjee ⁸³	No	MP 5000 mg				Kidney
Jeffery ⁵²	Yes	MP 5000 mg (+ CP)				Kidney
Souillou ⁵³	Yes	MP 5000 mg (+ CP)				Kidney
Corry ⁵⁴	No	MP 60 mg/kg (+ CP)				Kidney
Novitzky ⁵⁵	No	HC 100 mg (+ T3/IL)				
Taniguchi ⁵⁶	Yes	HC 3–5 mg/kg (+ T3)				
Follette ⁸⁴	No	MP 15 mg/kg		Lung	Lung	
Rosendale ⁸⁵	Yes	MP 15 mg/kg (+ AVP/T3/T4)				
Rosendale ⁶⁵	Yes	MP 15 mg/kg (+ AVP/ T3/T4)				
Van Bakel ⁶⁹	Yes	MP 1000–2000 mg (+ T4/IL)				
Salim ⁸⁶	No	MP 2000 mg × 1 (+ T4)				
Salim ⁸⁷	No	MP 2000 mg × 1 (+ T4)				
Kotsch ⁸⁸	No	MP 250 mg × 1, then 100 mg/hr				Liver
Venkateswaran ⁸⁹	Yes	MP 1000 mg (+ T3)		Lung		
Venkateswaran ⁹⁰	Yes	MP 1000 mg (+ T3)			Heart	
Nath ⁶⁶	Yes	MP 15 mg/kg (+ T4/AVP)				
Amatschek ⁹¹	No	MP 1000 mg				Liver
Dhar ⁹²	Yes	MP 15 mg/kg or HC 300 mg (+ T4)				
Pinsard ⁵⁷	No	HC 50 mg × 1, then 10 mg/hr				

AVP, arginine vasopressin; CP, cyclophosphamide; HC, hydrocortisone; IL, insulin; MP, methylprednisolone; T3, triiodothyronine; T4, thyroxine

* Green box indicates positive study results (improved outcome); yellow box indicates neutral study results (no difference); white box indicates outcome has not been assessed.

Table 3. Studies of Thyroid Hormone Replacement in Donor Management*

Reference	Pediatric Patients	Medication and Dosage	Outcomes				
			Improve Hemodynamics	Decrease Inotrope Use	Metabolic Changes†	Organ Recovery	Recipient Survival
Novitzky ⁵⁵	No	T3 2 mcg every hr (+ HC/IL)					
Randall ⁹³	No	T3 2 mcg/hr					
Taniguchi ⁵⁶	Yes	T3 1–1.5 mcg/kg/day (+ HC)					
Orlowski ⁶²	Yes	T4 20 mcg × 1, then 10 mcg/hr (+ MP/IL)					
Jeevanandam ⁶⁷	Yes	T3 0.2 mcg/kg every hr, up to 3 doses					Heart
Goarin ⁹⁴	Yes	T3 0.2 mcg/kg × 1					
Jeevanandam ⁶⁴	Yes	T3 0.6 mcg/kg × 1					
Roels ⁶⁸	No	T3 2–4 mcg/hr (+ HC/IL)					
Rosendale ⁸⁵	Yes	T3/T4 4 mcg/kg × 1, then 3 mcg/hr (+ MP/AVP)					
Rosendale ⁶⁵	Yes	T3/T4 4 mcg/kg × 1, then 3 mcg/hr (+ MP/AVP)					
Van Bakel ⁶⁹	Yes	T4 20 mcg × 1, then 10 mcg/hr (+ MP/IL)					
Zuppa ⁷⁰	Yes	T4 0.8–5 mcg/kg × 1, then 0.8–1.4 mcg/kg/hr					
Salim ⁸⁶	No	T4 20 mcg × 1, then 10 mcg/hr (+ MP/AVP/IL)					
Perez-Blanco ⁹⁵	No	T3 1 mcg/kg × 1, then 0.06 mcg/kg/hr					
Salim ⁶⁰	Yes	T4 20 mcg × 1, then 10 mcg/hr (+ MP/AVP/IL)					
Abdelnour ²⁰	Yes	T4 20 mcg × 1, then 10 mcg/hr (+ MP/IL)					
Venkateswaran ⁹⁰	Yes	T3 0.8 mcg/kg × 1, then 0.113 mcg/kg/hr (+ MP)					
Nath ⁶⁶	Yes	T4 20 mcg × 1, then 10 mcg/hr (+ MP/AVP/IL)					

AVP, arginine vasopressin; CP, cyclophosphamide; HC, hydrocortisone; IL, insulin; MP, methylprednisolone; T3, triiodothyronine; T4, thyroxine

* Green box indicates positive study results (improved outcome); yellow box indicates neutral study results (no difference); purple box indicates negative study results (worsened outcome); white box indicates outcome has not been assessed.

† Metabolic changes include acid-base balance (pH, base deficient, sodium bicarbonate concentrations) and/or serum lactate concentrations.

Table 4. Studies of Antidiuretic Hormone Replacement in Donor Management*

Study	Pediatric Patients	Medication and Dosage	Outcomes			
			Improve Hemodynamics	Decrease Vasopressor Use	Organ Recovery	Graft Function† Graft Survival
Iwai ⁷²	No	AVP 0.1–0.4 unit/hr (SD), AVP 1–2 unit/hr (LD)	LD			
Hirsch ⁹⁶	No	DDAVP 2 mcg every 6 hr				
Guesde ⁹⁷	No	DDAVP 1 mcg every 2 hr				
Katz ²⁷	Yes	AVP 0.041 unit/kg/hr ± 0.069				
Benck ⁹⁸	No	DDAVP 1–2 mcg × 1, then 0.5–1 mcg every 2–12 hr				
Plurad ⁷⁴	No	ND				
Callahan ⁹⁹	No	ND				

AVP, arginine vasopressin; DDAVP, desmopressin; LD, large dose; ND, not disclosed; SD, small dose; UOP, urine output
* Green box indicates positive study results (improved outcome); yellow box indicates neutral study results (no difference); red box indicates negative study results (worsened outcome); white box indicates outcome has not been assessed.
† Graft function is in reference to early renal function as measured by serum creatinine, urine output, and hemodialysis needs in the first 14 days after transplantation.

resulting in hyperdiuresis and subsequent hypovolemia leading to compromised hemodynamics.^{4,8,22}

There are two synthetic ADH analogues available, desmopressin and vasopressin, to supplement the loss of endogenous ADH. Desmopressin is similar to vasopressin in antidiuretic activity; however, replacing the L-arginine with D-arginine reduces the vasopressor activity of desmopressin. In addition, desmopressin has a de-aminated cysteine residue at the end of the compound that prolongs the half-life compared with vasopressin.

Pediatric evidence supporting ADH replacement in donor management is limited, although vasopressin is routinely used in the treatment of DI as well as catecholamine-refractory shock in critically ill children. Vasopressin in organ donors has been associated with improved hemodynamics and decreasing the need for vasoactive agents (Table 4).^{27,72,73} Additionally, vasopressin-treated patients have been reported to produce more high-yield donations of 4 or more organs, specifically heart donations, when compared with the vasopressin-naïve donors.⁷⁴ Vasopressin is recommended for use in donor children for DI management and in combination with other hormonal replacement therapies to provide stability prior to organ recovery.¹³

Other Donor Management Controversies —

Extracorporeal Membrane Oxygenation and Organ Donors. Extracorporeal membrane oxygenation (ECMO) is a therapy used in critically ill children and may be used in premortem and postmortem management of the organ donor. Children may progress to brain death while receiving ECMO support. Unfortunately, ECMO support does complicate the brain death clinical exam, making it more difficult to complete and be considered for DNDD. Literature has described a 22% successful completion rate of the apnea test in ECMO patients compared with 72% in non-ECMO patients.⁷⁵ Nonetheless, in hemodynamically unstable donors, ECMO may serve as a bridge to provide physiologic stability until procurement. A small retrospective study reported no functional or survival difference in kidney grafts recovered from brain-dead ECMO donors compared with non-ECMO donors.⁷⁶ Postmortem ECMO support may be considered in the DCDD patient in order to expand the donor pool. Organs recovered from DCDD patients experience warm ischemic injury, which adversely affects graft survival and results in a greater risk of complications after transplantation. Extracorporeal membrane oxygenation can provide a period of normothermic regional perfusion that may avoid warm ischemic effects and improve organ function. In the case of postmortem ECMO, cannulation occurs before the removal of life-sustaining therapies. After circulatory death is declared, ECMO is provided with a supradiaphragmatic aortic occlusion balloon *in situ* to allow regional perfusion to the abdominal

Table 5. Position Papers and Policy Statements

Date	Policy Statement
1997	IOM Non-Heart-Beating Organ Transplantation: Medical and Ethical Issues in Procurement ¹⁰⁰
2000	IOM Non-Heart-Beating Organ Transplantation: Practice and Protocols ¹⁰¹
2001	SCCM Recommendations for Nonheartbeating Organ Donation ¹⁰²
2004	TJC Health Care at the Crossroads: Strategies for Narrowing the Organ Donation Gap and Protecting Patients ¹⁰³
2006	CCDT Organ Donor Management in Canada: Recommendations of the Forum of Medical Management to Optimize Donor Organ Potential ²³
2007	NATCO Pediatric Donor Management and Dosing Guidelines ⁸²
2010	AAP Policy Statement—Pediatric Organ Donation and Transplantation ¹⁰⁴
2013	ATS/ISHLT/SCCM/AOPO/UNOS Statement: Ethical and Policy Considerations in Organ Donation after Circulatory Determination of Death ¹⁰⁵
2015	SCCM/ACCP/AOPO Consensus Statement: Management of the Potential Organ Donor in the ICU ¹³
2017	Canadian Guidelines for Controlled Pediatric Donation after Circulatory Determination of Death—Summary Report ¹⁰⁶

AAP, American Academy of Pediatrics; ACCP, American College of Chest Physicians; AOPO, Association of Organ Procurement Organizations; ATS, American Thoracic Society; CCDT, Canadian Council for Donation and Transplantation; IOM, Institute of Medicine; ISHLT, International Society for Heart & Lung Transplantation; NATCO, North American Transplant Coordinators Organization; SCCM, Society of Critical Care Medicine; TJC, The Joint Commission; UNOS, United Network for Organ Sharing

cavity organs and avoiding reperfusion of the heart and brain.⁷⁷ Postmortem ECMO in the DCDD patient is rich with ethical dilemmas that include premortem cannulation, which may inflict pain on or harm to the patient, premortem heparinization that may hasten death, possible postmortem reperfusion of the heart and brain leading to autoresuscitation, and whether the reperfusion provided by ECMO circulation constitutes reinstatement of circulatory function.^{77,78} Preliminary reports of postmortem ECMO describe similar kidney and liver graft survival and recipient survival compared with DNDD groups.⁷⁹ However, further study of postmortem ECMO for organ recovery in DCDD patients is recommended before widespread acceptance and implementation.¹³

Infection. Donor infections are not absolute contraindications for organ recovery. Some infections are precluded, such as viral meningitis, fungal infections, and active hepatitis B; otherwise, most bacterial infec-

tions can be treated with appropriate antibiotics in the donor and can continue treatment in the recipient to complete the course. Culture-driven antibiotics are recommended for a minimum of 48 hours in the donor patient before organ recovery.¹³ Antibiotic prophylaxis is typically not recommended, with the exception that most centers do perform bowel decontamination prior to small bowel recovery. Each OPO is recommended to develop a protocol for antibiotic prophylaxis, including agent selection and trigger for initiating antimicrobials based on local practices and antibiograms.¹³

Enteral Nutrition. There is no OPTN policy or recommendation on feeding or fasting in DNDD patients. It is a common practice to stop enteral nutrition after declaration of brain death because of the assumed lower metabolic needs, issues with insulin resistance, and carbohydrate metabolism. A randomized open-label trial of brain-dead organ donors revealed no difference in all-cause recipient mortality at 6 months regardless of

Table 6. Donor Management Resources

National Organizations	Website	Resources
Association of Organ Procurement Organizations (AOPO)	http://www.aopo.org/	Organ Procurement Organizations resources, organ donor management guidelines
American Society of Transplant Surgeons (ASTS)	https://asts.org/	Advocacy materials, provider education, research grants
Organ Procurement and Transplantation Network (OPTN)	https://optn.transplant.hrsa.gov/	Data sets and policies
The Organ Donation and Transplantation Alliance	https://organdonationalliance.org/	Provider education, organ donor management resources
United Network for Organ Sharing (UNOS)	https://transplantpro.org/	Patient and provider education, organ and patient safety resources, policies

feeding status at time of organ recovery, but an increase in resting energy expenditures in donors who received corticosteroids was noted.⁸⁰ Animal models have demonstrated gut mucosa and villus height decline within 12 hours of the fasting state before organ recovery.⁸¹ Therefore, enteral feeding may be considered during the donor management period to preserve small bowel function in the potential small bowel donor.¹³

Conclusion

There are distinct physiologic changes that occur after declaration of death. A number of therapeutic strategies may be used to mitigate the harm to the organs and increase organ viability, including pharmacologic hemodynamic support, hormone replacement therapy, and considerations for antimicrobials and nutrition. Many resources are available to assist the pediatric pharmacist in making informed decisions for the management of the pediatric organ donor (Tables 5 and 6). The OPOs will direct which medication to use in management of the pediatric donor patient, but the pediatric pharmacist remains the medication expert who can help inform and influence the local OPO medication protocols.

ARTICLE INFORMATION

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REFERENCES

- Nakagawa TA, Ashwal S, Mathur M, Mysore M. Clinical report-guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. *Pediatrics*. 2011;128(3):e720–e740.
- Nakagawa TA, Ashwal S, Mathur M, et al. Guidelines for the determination of brain death in infants and children: an update of the 1987 Task Force recommendations. *Critical Care Med*. 2011;39(9):2139–2155.
- Halazun KJ, Al-Mukhtar A, Aldouri A, et al. Warm ischemia in transplantation: search for a consensus definition. *Transplant Proc*. 2007;39(5):1329–1331.
- Dictus C, Vienenkoetter B, Esmaeilzadeh M, et al. Critical care management of potential organ donors: our current standard. *Clin Transplant*. 2009;21(23 suppl):2–9.
- Smith M. Physiologic changes during brain stem death—lessons for management of the organ donor. *J Heart Lung Transplant*. 2004;23(9 suppl):S217–S222.
- Ranasinghe AM, Bonser RS. Endocrine changes in brain death and transplantation. *Best Pract Res Clin Endocrinol Metab*. 2011;25(5):799–812.
- Dimopoulou I, Tsagarakis S, Anthi A, et al. High prevalence of decreased cortisol reserve in brain-dead potential organ donors. *Critical Care Med*. 2003;31(4):1113–1117.
- Phongsamran PV. Critical care pharmacy in donor management. *Prog Transplant*. 2004;14(2):105–111.
- Wood KE, Becker BN, McCartney JG, et al. Care of the potential organ donor. *N Engl J Med*. 2004;351(26):2730–2739.
- Mojtabae M, Sadegh Beigee F, Ghorbani F. Deceased organ donation from pediatric donors: does the literature really help us?: implication for more powerful guidelines. *Transplant Proc*. 2017;49(8):1708–1711.
- Gores PF, Gillingham KJ, Dunn DL, et al. Donor hyperglycemia as a minor risk factor and immunologic variables as major risk factors for pancreas allograft loss in a multivariate analysis of a single institution's experience. *Ann Surg*. 1992;215(3):217–230.
- Latifi S, Lebovitz D. Pediatric donor management. Association of Organ Procurement Organizations, 2013. <http://www.aopo.org/wikidonor/donor-management/pediatric-donor/>. Accessed February 19, 2019.
- Kotloff RM, Blosser S, Fulda GJ, et al. 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. *Crit Care Med*. 2015;43(6):1291–1325.
- Health Resources and Services Administration. Policies. US Department of Health & Human Services, 2018. <https://optn.transplant.hrsa.gov/governance/policies/>. Accessed February 19, 2019.
- Foster BA, Tom D, Hill V. Hypotonic versus isotonic fluids in hospitalized children: a systematic review and meta-analysis. *J Pediatr*. 2014;165(1):163–169.
- Carandang F, Anglemyer A, Longhurst CA, et al. Association between maintenance fluid tonicity and hospital-acquired hyponatremia. *J Pediatr*. 2013;163(6):1646–1651.
- Friedman JN, Beck CE, DeGroot J, et al. Comparison of isotonic and hypotonic intravenous maintenance fluids: a randomized clinical trial. *JAMA Pediatr*. 2015;169(5):445–451.
- McNab S, Ware RS, Neville KA, et al. Isotonic versus hypotonic solutions for maintenance intravenous fluid administration in children. *Cochrane Database Syst Rev*. 2014;(12):CD009457.
- Pennefather SH, Bullock RE, Dark JH. The effect of fluid therapy on alveolar arterial oxygen gradient in brain-dead organ donors. *Transplantation*. 1993;56(6):1418–1422.

20. Abdelnour T, Rieke S. Relationship of hormonal resuscitation therapy and central venous pressure on increasing organs for transplant. *J Heart Lung Transplant*. 2009;28(5):480–485.
21. Miñambres E, Rodrigo E, Ballesteros MA, et al. Impact of restrictive fluid balance focused to increase lung procurement on renal function after kidney transplantation. *Nephrol Dial Transplant*. 2010;25(7):2352–2356.
22. Chamorro C, Falcon JA, Michelena JC. Controversial points in organ donor management. *Transplant Proc*. 2009;41:3473–3475.
23. Shemie SD, Ross H, Pagliarello J, et al. Organ donor management in Canada: recommendations of the forum on medical management to optimize donor organ potential. *CMAJ*. 2006;174(6):S13–S32.
24. Audibert G, Charpentier C, Seguin-Devaux C, et al. Improvement of donor myocardial function after treatment of autonomic storm during brain death. *Transplantation*. 2006;82(8):1031–1036.
25. Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. *Crit Care Med*. 2017;45(6):1061–1093.
26. D'Amico TA, Meyers CH, Koutlas TC, et al. Desensitization of myocardial beta-adrenergic receptors and deterioration of left ventricular function after brain death. *J Thorac Cardiovasc Surg*. 1995;110(3):746–751.
27. Katz K, Lawler J, Wax J, et al. Vasopressin pressor effects in critically ill children during evaluation for brain death and organ recovery. *Resuscitation*. 2000;47(1):33–40.
28. Schnuelle P, Berger S, de Boer J, et al. Effects of catecholamine application to brain-dead donors on graft survival in solid organ transplantation. *Transplantation*. 2001;72(3):455–463.
29. Schnuelle P, Lorenz D, Mueller A, et al. Donor catecholamine use reduces acute allograft rejection and improves graft survival after cadaveric renal transplantation. *Kidney Int*. 1999;56(2):738–746.
30. Schnuelle P, Yard BA, Braun C, et al. Impact of donor dopamine on immediate graft function after kidney transplantation. *Am J Transplant*. 2004;4(3):419–426.
31. Schnuelle P, Schmitt WH, Weiss C, et al. Effects of dopamine donor pretreatment on graft survival after kidney transplantation: a randomized trial. *Clin J Am Soc Nephrol*. 2017;12(3):493–501.
32. Angleitner P, Kaider A, Gokler J, et al. High-dose catecholamine donor support and outcomes after heart transplantation. *J Heart Lung Transplant*. 2018;37(5):596–603.
33. Totsuka E, Dodson F, Urakami A, et al. Influence of high donor serum sodium levels on early postoperative graft function in human liver transplantation: effect of correction of donor hyponatremia. *Liver Transpl Surg*. 1999;5(5):421–428.
34. Totsuka E, Fung U, Hakamada K, et al. Analysis of clinical variables of donors and recipients with respect to short-term graft outcome in human liver transplantation. *Transplant Proc*. 2004;36(8):2215–2218.
35. Kaseje N, Luthold S, Mentha G, et al. Donor hyponatremia influences outcomes following pediatric liver transplantation. *Eur J Pediatr Surg*. 2013;23(1):8–13.
36. Kaseje N, McLin V, Toso C, et al. Donor hyponatremia before procurement and early outcomes following pediatric liver transplantation. *Liver Transpl*. 2015;21(8):1076–1081.
37. Adroge HJ, Madias NE. Hyponatremia. *N Engl J Med*. 2000;342(20):1493–1499.
38. Pierce LR, Gaines A, Varricchio F, Epstein J. Hemolysis and renal failure associated with use of sterile water for injection to dilute 25% human albumin solution. *Am J Health Syst Pharm*. 1998;55(10):1057, 1062, 1070.
39. Centers for Disease Control and Prevention. Hemolysis associated with 25% human albumin diluted with sterile water—United States, 1994–1998. *MMWR Morb Mortal Wkly Rep*. 1999;48(8):157–159.
40. Krzyzaniak JF, Alvarez Nunez FA, Raymond DM, Yalkowsky SH. Lysis of human red blood cells, 4: Comparison of in vitro and in vivo hemolysis data. *J Pharm Sci*. 1997;86(11):1215–1217.
41. Krzyzaniak JF, Raymond DM, Yalkowsky SH. Lysis of human red blood cells, 1: effect of contact time on water induced hemolysis. *PDA J Pharm Sci Technol*. 1996;50(4):223–226.
42. Ramaswamykanive H, Greaves J. Intravenous infusion of sterile water for the treatment of hyponatraemia. *Anaesth Intensive Care*. 2014;42(2):258–262.
43. Masson F, Thicoipe M, Gin H, et al. The endocrine pancreas in brain-dead donors: a prospective study in 25 patients. *Transplantation*. 1993;56(2):363–367.
44. Blasi-Ibanez A, Hirose R, Feiner J, et al. Predictors associated with terminal renal function in deceased organ donors in the intensive care unit. *Anesthesiology*. 2009;110(2):333–341.
45. Parekh J, Niemann CU, Dang K, Hirose R. Intraoperative hyperglycemia augments ischemia reperfusion injury in renal transplantation: a prospective study. *J Transplant*. 2011;2011:652458.
46. Agus MS, Wypij D, Hirshberg EL, et al. Tight glycemic control in critically ill children. *N Engl J Med*. 2017;376(8):729–741.
47. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354(5):449–461.
48. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345(19):1359–1367.
49. Preiser JC, Devos P, Ruiz-Santana S, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med*. 2009;35(10):1738–1748.
50. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283–1297.
51. Novitzky D, Mi Z, Videla LA, et al. Hormone resuscitation therapy for brain-dead donors -- is insulin beneficial or detrimental? *Clin Transplant*. 2016;30(7):754–759.
52. Jeffery JR, Downs A, Grahame JW, et al. A randomized prospective study of cadaver donor pretreatment in renal transplantation. *Transplantation*. 1978;25(6):287–289.
53. Souillou JP, Baron D, Rouxel A, Guenel J. Steroid-cyclophosphamide pretreatment of kidney allograft donors: a control study. *Nephron*. 1979;24(4):193–197.
54. Corry RJ, Patel NP, West JC, Schanbacher BA. Pretreatment of cadaver donors with cyclophosphamide and methylprednisolone: effect on renal transplant outcome. *Transplant Proc*. 1980;12(2):348–351.

55. Novitzky D, Cooper DK, Reichart B. Hemodynamic and metabolic responses to hormonal therapy in brain-dead potential organ donors. *Transplantation*. 1987;43(6):852–854.
56. Taniguchi S, Kitamura S, Kawachi K, et al. Effects of hormonal supplements on the maintenance of cardiac function in potential donor patients after cerebral death. *Eur J Cardiothorac Surg*. 1992;6(2):96–101.
57. Pinsard M, Ragot S, Mertes PM, et al. Interest of low-dose hydrocortisone therapy during brain-dead organ donor resuscitation: the CORTICOME study. *Crit Care*. 2014;18(4):R158.
58. Kuecuk O, Mantouvalou L, Klemz R, et al. Significant reduction of proinflammatory cytokines by treatment of the brain-dead donor. *Transplant Proc*. 2005;37(1):387–388.
59. Dupuis S, Amiel JA, Desgroseilliers M, et al. Corticosteroids in the management of brain-dead potential organ donors: a systematic review. *Br J Anaesth*. 2014;113(3):346–359.
60. Salim A, Martin M, Brown C, et al. Using thyroid hormone in brain-dead donors to maximize the number of organs available for transplantation. *Clin Transplant*. 2007;21(3):405–409.
61. Novitzky D, Cooper DK, Chaffin JS, et al. Improved cardiac allograft function following triiodothyronine therapy to both donor and recipient. *Transplantation*. 1990;49(2):311–316.
62. Orłowski JP, Spees EK. Improved cardiac transplant survival with thyroxine treatment of hemodynamically unstable donors: 95.2% graft survival at 6 and 30 months. *Transplant Proc*. 1993;25(1, pt 2):1535.
63. Wheeldon DR, Potter CD, Oduro A, et al. Transforming the “unacceptable” donor: outcomes from the adoption of a standardized donor management technique. *J Heart Lung Transplant*. 1995;14(4):734–742.
64. Jeevanandam V. Triiodothyronine: spectrum of use in heart transplantation. *Thyroid*. 1997;7(1):139–145.
65. Rosendale JD, Kauffman HM, McBride MA, et al. Hormonal resuscitation yields more transplanted hearts, with improved early function. *Transplantation*. 2003;75(8):1336–1341.
66. Nath DS, Ilias Basha H, Liu MH, et al. Increased recovery of thoracic organs after hormonal resuscitation therapy. *J Heart Lung Transplant*. 2010;29(5):594–596.
67. Jeevanandam V, Todd B, Regillo T, et al. Reversal of donor myocardial dysfunction by triiodothyronine replacement therapy. *J Heart Lung Transplant*. 1994;13(4):681–687.
68. Roels L, Pirenne J, Delooz H, et al. Effect of triiodothyronine replacement therapy on maintenance characteristics and organ availability in hemodynamically unstable donors. *Transplant Proc*. 2000;32(7):1564–1566.
69. Van Bakel AB, Pitzer S, Drake P, et al. Early hormonal therapy stabilizes hemodynamics during donor procurement. *Transplant Proc*. 2004;36(9):2573–2578.
70. Zuppa AF, Nadkarni V, Davis L, et al. The effect of a thyroid hormone infusion on vasopressor support in critically ill children with cessation of neurologic function. *Crit Care Med*. 2004;32(11):2318–2322.
71. Zaroff JG, Rosengard BR, Armstrong WF, et al. Consensus conference report: maximizing use of organs recovered from the cadaver donor: cardiac recommendations, March 28–29, 2001, Crystal City, Va. *Circulation*. 2002;106(7):836–841.
72. Iwai A, Sakano T, Uenishi M, et al. Effects of vasopressin and catecholamines on the maintenance of circulatory stability in brain-dead patients. *Transplantation*. 1989;48(4):613–617.
73. Pennefather SH, Bullock RE, Mantle D, Dark JH. Use of low dose arginine vasopressin to support brain-dead organ donors. *Transplantation*. 1995;59(1):58–62.
74. Plurad DS, Bricker S, Neville A, et al. Arginine vasopressin significantly increases the rate of successful organ procurement in potential donors. *Am J Surg*. 2012;204(6):856–860.
75. Bronchard R, Durand L, Legeai C, et al. Brain-dead donors on extracorporeal membrane oxygenation. *Critical Care Med*. 2017;45(10):1734–1741.
76. Carter T, Bodzin AS, Hirose H, et al. Outcome of organs procured from donors on extracorporeal membrane oxygenation support: an analysis of kidney and liver allograft data. *Clin Transplant*. 2014;28(7):816–820.
77. Dalle Ave AL, Shaw DM, Bernat JL. Ethical issues in the use of extracorporeal membrane oxygenation in controlled donation after circulatory determination of death. *Am J Transplant*. 2016;16(8):2293–2299.
78. DeJohn C, Zwischenberger JB. Ethical implications of extracorporeal interval support for organ retrieval (EISOR). *ASAIO J*. 2006;52(2):119–122.
79. Shapey IM, Muiesan P. Regional perfusion by extracorporeal membrane oxygenation of abdominal organs from donors after circulatory death: a systematic review. *Liver Transpl*. 2013;19(12):1292–1303.
80. Hergenroeder GW, Ward NH, Yu X, et al. Randomized trial to evaluate nutritional status and absorption of enteral feeding after brain death. *Prog Transplant*. 2013;23(4):374–382.
81. Salehi P, Churchill TA. The influence of short-term fasting on the quality of small bowel graft preservation. *Cryobiology*. 2005;50(1):83–92.
82. North American Transplant Coordinators Organization. Donor Management and Dosing Guidelines. 2007. <http://www.organdonationalliance.org/wp-content/uploads/toolbox.v.2/NATCOPedDonorManagementGuidelines1-odt.pdf>. Accessed February 19, 2019.
83. Chatterjee SN, Terasaki PI, Fine S, et al. Pretreatment of cadaver donors with methylprednisolone in human renal allografts. *Surg Gynecol Obstet*. 1977;145(5):729–732.
84. Follette DM, Rudich SM, Babcock WD. Improved oxygenation and increased lung donor recovery with high-dose steroid administration after brain death. *J Heart Lung Transplant*. 1998;17(4):423–429.
85. Rosendale JD, Kauffman HM, McBride MA, et al. Aggressive pharmacologic donor management results in more transplanted organs. *Transplantation*. 2003;75(4):482–487.
86. Salim A, Velmahos GC, Brown C, et al. Aggressive organ donor management significantly increases the number of organs available for transplantation. *J Trauma*. 2005;58(5):991–994.
87. Salim A, Martin M, Brown C, et al. The effect of a protocol of aggressive donor management: implications for the national organ donor shortage. *J Trauma*. 2006;61(2):429–433.
88. Kotsch K, Ulrich F, Reutzel-Selke A, et al. Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver

- transplantation: a prospective randomized controlled trial. *Ann Surg*. 2008;248(6):1042–1050.
89. Venkateswaran RV, Patchell VB, Wilson IC, et al. Early donor management increases the retrieval rate of lungs for transplantation. *Ann Thorac Surg*. 2008;85(1):278–286.
  90. Venkateswaran RV, Steeds RP, Quinn DW, et al. The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-blind factorially designed controlled trial. *Eur Heart J*. 2009;30(14):1771–1780.
  91. Amatschek S, Wilflingseder J, Pones M, et al. The effect of steroid pretreatment of deceased organ donors on liver allograft function: a blinded randomized placebo-controlled trial. *J Hepatol*. 2012;56(6):1305–1309.
  92. Dhar R, Cotton C, Coleman J, et al. Comparison of high- and low-dose corticosteroid regimens for organ donor management. *J Crit Care*. 2013;28(1):11.e1–e7.
  93. Randall TT, Höckerstedt KA. Triiodothyronine treatment in brain-dead multiorgan donor—a controlled study. *Transplantation*. 1992;54(4):736–738.
  94. Goarin JP, Cohen S, Riou B, et al. The effects of triiodothyronine on hemodynamic status and cardiac function in potential heart donors. *Anesth Analg*. 1996;83(1):41–47.
  95. Perez-Blanco A, Caturla-Such J, Canovas-Robles J, Sanchez-Paya J. Efficiency of triiodothyronine treatment on organ donor hemodynamic management and adenine nucleotide concentration. *Intensive Care Med*. 2005;31(7):943–948.
  96. Hirschl MM, Matzner MP, Huber WO, et al. Effect of desmopressin substitution during organ procurement on early renal allograft function. *Nephrol Dial Transplant*. 1996;11(1):173–176.
  97. Guesde R, Barrou B, Leblanc I, et al. Administration of desmopressin in brain-dead donors and renal function in kidney recipients. *Lancet*. 1998;352(9135):1178–1181.
  98. Benck U, Gottmann U, Hoeger S, et al. Donor desmopressin is associated with superior graft survival after kidney transplantation. *Transplantation*. 2011;92(11):1252–1258.
  99. Callahan DS, Neville A, Bricker S, et al. The effect of arginine vasopressin on organ donor procurement and lung function. *J Surg Res*. 2014;186(1):452–457.
  100. Potts JT Jr, Herdman R. *Non-Heart-Beating Organ Transplantation: Medical and Ethical Issues in Procurement*. Washington, DC: National Academies Press; 1997.
  101. Institute of Medicine Committee on Non-Heart-Beating Transplantation IITS. *Non-Heart-Beating Organ Transplantation: Practice and Protocols*. Washington, DC: National Academies Press; 2000.
  102. DeVita MA, Webb SA, Hurford WE, et al. Recommendations for nonheartbeating organ donation. A position paper by the Ethics Committee, American College of Critical Care Medicine, Society of Critical Care Medicine. *Crit Care Med*. 2001;29(9):1826–1831.
  103. The Joint Commission. Strategies for narrowing the organ donation gap and protecting patients. 2004. https://www.jointcommission.org/assets/1/18/organ_donation_white_paper.pdf/. Accessed February 19, 2019.
  104. American Academy of Pediatrics. Policy statement—pediatric organ donation and transplantation. *Pediatrics*. 2010;125(4):822–828.
  105. Gries CJ, White DB, Truog RD, et al. An official American Thoracic Society/International Society for Heart and Lung Transplantation/Society of Critical Care Medicine/Association of Organ and Procurement Organizations/United Network of Organ Sharing statement: ethical and policy considerations in organ donation after circulatory determination of death. *Am J Respir Crit Care Med*. 2013;188(1):103–109.
  106. Weiss MJ, Hornby L, Rochweg B, et al. Canadian guidelines for controlled pediatric donation after circulatory determination of death—summary report. *Pediatr Crit Care Med*. 2017;18(11):1035–1046.