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Abstract

Brain death is associated with complex physiologic changes that may impact the management of the potential organ donor. Medical management is critical to actualizing the individual or family's intent to donate and maximizing the benefit of that intent. This interval of care in the PICU begins with brain death and consent to donation and culminates with surgical organ procurement. During this phase, risks for hemodynamic instability and compromise of end organ function are high. The brain dead organ donor is in a distinct and challenging pathophysiologic condition that culminates in multifactorial shock. The potential benefits of aggressive medical management of the organ donor may include increased number of donors providing transplantable organs and increased number of organs transplanted per donor. This may improve graft function, graft survival, and patient survival in those transplanted. In this chapter, pathophysiologic changes occurring after brain death are reviewed. General and organ specific donor management strategies and logistic considerations are discussed. There is a significant opportunity for enhancing donor multi-organ function and improving organ utilization with appropriate PICU management.

Keywords

Brain death • Brainstem death • Organ donation • Donor management • Organ yield

Introduction

Successful medical management of the organ donor is critical to actualizing the individual or family's intent to donate and maximizing the benefit of that intent. This interval of care in the PICU begins with brain death and consent to donation and culminates with surgical organ procurement. It generally ranges from 12 to 48 h or longer and is related to the

time required for repeated brain death declarations, consent discussions with the family, procurement logistics of donor/organ evaluation, and donor/recipient matching. During this phase, risks for hemodynamic instability and compromise of end organ function are high (Table 38.1). There is a significant opportunity for enhancing donor multi-organ function and improving organ utilization with appropriate medical management [1].

The brain dead organ donor is in a distinct and challenging pathophysiological condition that culminates in a state of multifactorial shock. The current level of evidence supporting practices in pediatric donor management is limited by the inherent lack of prospective trial data, and based largely on adult human and animal studies; however, donor management practice is of increasing importance [2–5]. PICU care should be tailored by principles similar to the management of any patient with multifactorial shock. It is important to treat the donor as one would treat the transplant recipient.

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This can be accomplished by understanding the physiology of brain death coupled with aggressive and attentive PICU management.

Figure 38.1 shows the Canadian experience of organ utilization across all age groups, comparable to international rates [6–8]. Utilization rates vary from region to region and transplant center to transplant center. Rates for heart and lung utilization have the greatest capacity for quantitative improvement. For the purposes of most international reports, a “donor” is one who has provided at least one organ that has been transplanted (Table 38.2). Initial interventions to increase transplantation focused on identification, referral, and consent of the donor, recent pursuit of organ yield has

gained importance [9]. Pediatric investigators have reported rates of 3.6 organs per donor (of eight possible organs), but 22 % of consented pediatric donors failed to provide *any* transplantable organs primarily due to hemodynamic instability during the phase of PICU donor care [10].

The goal of PICU based donor management is to improve the utilization of organs from consented donors to transplant recipients. The potential benefits of aggressive medical management of the organ donor may include increased number of donors providing transplantable organs and increased number of organs transplanted per donor. This may improve graft function, graft survival and patient survival in those transplanted [11].

Table 38.1 Incidence of pathophysiologic changes occurring after brain stem death requiring intensive care management of the potential organ donor

Hypotension	81 %
Diabetes insipidus	65 %
Disseminated intravascular coagulation	28 %
Cardiac arrhythmias	25 %
Pulmonary edema	18 %
Metabolic acidosis	11 %

[Based on data from ref. 298]

Table 38.2 Organ-specific donation numbers for pediatric deceased brain dead donors in United States, UNOS

	2010	2009
All donors	841	916
Kidney	792	854
Liver	739	794
Heart	477	480
Pancreas	321	365
Lung	212	204
Intestine	100	138

[Based on data from Ref. 299]

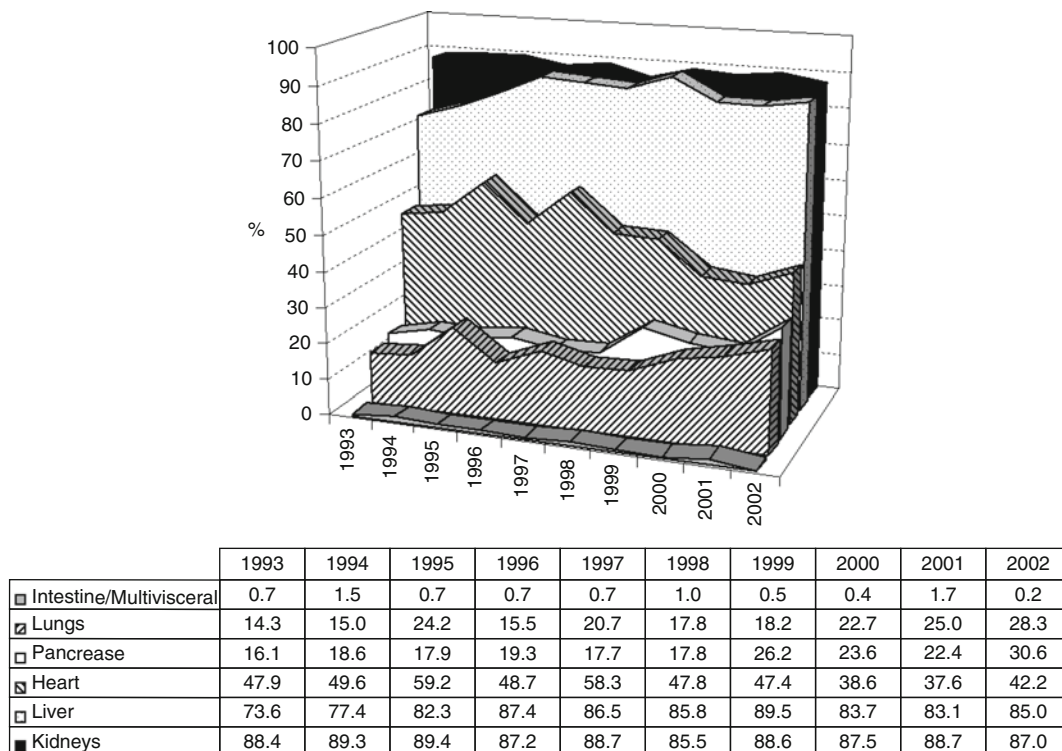


Fig. 38.1 Organ-specific utilization rates for deceased donors, Canada, 1993–2002 (Reprinted from Badovinac et al. [6]. With permission from Springer Science + Business Media.)

The Physiology of Brain Death

The deterioration of cardiovascular and pulmonary function associated with intracranial hypertension will vary with the rapidity of rise of intracranial pressure (ICP) [12], time after herniation, and presence of coexisting forms of myocardial injury e.g., traumatic myocardial contusion, ischemia after cardiac arrest, shock, or hypoxemia [13, 14]. In the face of markedly elevated ICP, mean arterial pressure (MAP) rises in an effort to maintain cerebral perfusion pressure. As ICP rises further, cerebral herniation into the brainstem ensues, and brainstem ischemia is initiated in an orderly, rostral-caudal fashion. Initial apnea, bradycardia, hypotension and drop in cardiac output are mediated by vagal (parasympathetic) activation resulting from midbrain ischemia. Brainstem ischemia then progresses toward the pons, where sympathetic stimulation is superimposed on the initial vagal response, resulting in bradycardia and hypertension (the classic Cushing's reflex) [15]. During this period, the ECG may be characterized by sinus bradycardia, junctional escape beats, and even complete heart block [16]. Further extension into the medulla oblongata occurs, at which point the vagal cardiomotor nucleus becomes ischemic, preventing tonic vagal stimuli. This results in unopposed sympathetic stimulation which may last for minutes to hours and manifests as arterial hypertension with elevated cardiac output with the potential for tachyarrhythmias [16]. This period of unopposed sympathetic stimulation is often termed the "autonomic" or "sympathetic storm" during which time cardiotoxicity occurs and severe vasoconstriction may compromise end organ perfusion [17, 18]. Subsequent changes occur in oxygen consumption and delivery [19]. Herniation triggers an inflammatory cascade that affects cardiorespiratory function, and hormonal regulation [20]. This cascade affects pituitary and hypothalamic function resulting in catecholamine, thyroid, and vasopressin abnormalities [21–24].

Neurogenic Myocardial Dysfunction

The sympathetic storm is responsible for potentially reversible myocardial injury and has been best studied in subarachnoid hemorrhage [25], where it is called "neurogenically stunned myocardium" [26, 27]. Endogenous catecholamine-related increases in peripheral resistance may result in a sudden increase in myocardial work and oxygen consumption leading to myocardial ischemia or infarction and subsequent elevation of cardiac troponin I and T [15, 28]. Patients dying of acute intracranial events show scattered foci of transmural myocardial injury that are not seen in patients dying of non-cerebral causes [29]. Myocardial necrosis after subarachnoid hemorrhage is a neurally mediated process that is dependent on the severity of neurological injury [30]. Brain dead

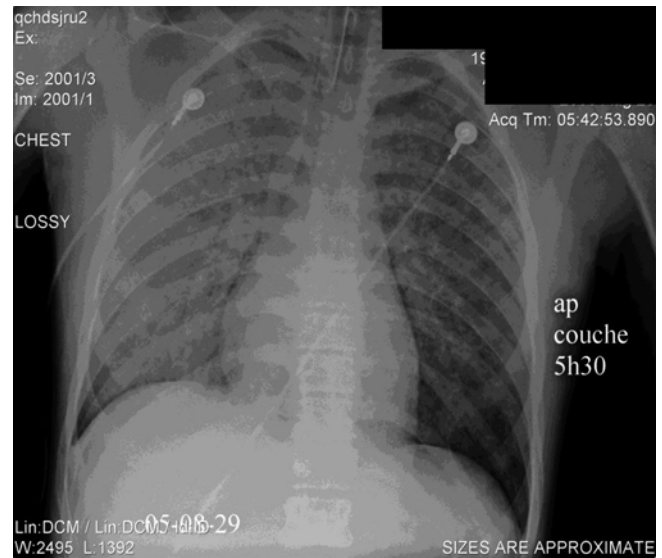


Fig. 38.2 Chest x-ray showing neurogenic pulmonary edema in an adolescent with acute intracranial hypertension

cardiac donors with elevations in cardiac troponin I have been shown to have diffuse subendocardial myocytolysis and coagulative necrosis and a high incidence of graft failure after transplantation [31]. The magnitude of the rise of epinephrine after brain death and the extent of myocardial damage have also been shown to depend on the rate of rise in ICP in a canine model [12, 32]. Dogs given a sudden rise in ICP demonstrated a higher epinephrine surge and poorly functioning donor hearts. Surgical sympathectomy [33] or pharmacologic sympathetic blockade in humans [34] and animals [35, 36] effectively prevents the ICP-related catecholamine cardiotoxicity and the electrophysiologic, biochemical and pathologic changes characteristic of neurogenic injury in the heart. While the ICP-related sympathetic storm is characterized by myocardial injury and high systemic vascular resistance, it is soon followed by period of sympathetic depletion and a low SVR state. Brain dead patients become functionally decapitated and the sympathetic system is anatomically interrupted, similar to high spinal cord injuries [37].

Neurogenic Pulmonary Edema

This unopposed sympathetic stimulation mediates the myocardial injury and is also likely responsible for the neurogenic pulmonary edema often seen in the management of patients with acute elevations of ICP (Fig. 38.2) [38]. Practitioners should be aware of this fulminant presentation of sudden onset respiratory failure with large volume, frothy tracheal secretions. In primate models of acute intracranial hypertension, acute heart failure ensues with reversal of flow in the pulmonary circulation due to massive rises in left atrial

pressure [33]. Rupture of pulmonary capillaries can occur from this retrograde increase in vascular hydrostatic pressure [39]. This hydrostatic pulmonary edema is responsive to high PEEP and is generally reversible with time [40, 41].

Inflammatory State

Brain death is also associated with the up-regulation and induction of the inflammatory response in all somatic organs [42], triggering a cascade of mediators that may affect graft function [43]. Transient focal cerebral ischemia upregulates the transcriptional levels of TNF- α , IL-6, and other markers [44, 45]. Rapid rises of ICP causes immune activation in peripheral organs resulting in enhanced immunogenicity [32]. In animal models, brain death has a detrimental effect on hepatic dysfunction related to immune activation and appears to be independent of hemodynamic instability [46] and magnified by longer ischemic times [47]. In comparison to living related kidney donors, kidneys from brain dead donors have significantly higher levels of pro-inflammatory mediators on biopsy (endothelial E-selectin and proximal tubular expression of HLA-DR antigens, intracellular adhesion molecule-1, and vascular cell adhesion molecule-1) [48, 49]. Delayed renal graft function and acute rejection in the recipient is correlated to higher indices of free radical mediated injury in the donor [50, 51]. Evidence that neurogenic pulmonary edema may be alleviated with glucocorticoids also suggests that an inflammatory component exists in this process [52, 53]. Recent animal work suggests that this inflammation is triggered by the acute hemodynamic effects of ICP-related neurogenic myocardial dysfunction, resulting in hydrostatic pressure based neurogenic pulmonary edema and rupture of the alveolar-capillary membrane [39, 54].

Brain death is an important risk factor itself and influences graft outcomes, mediated by postischemic reperfusion injury and other nonantigen-dependent inflammatory pathways [55, 56]. Deleterious processes such as inflammation and fibrosis occur in donor organs [57] potentiating graft immunogenicity and increases host alloresponsiveness organs, developing and contributing to reduced graft survival [58]. These findings may be used to introduce specific cytoprotective interventions in the brain dead donor to reduce the immunogenicity or the pro-inflammatory status of the graft and better maintain or increase organ viability. Anti-inflammatory therapies may be beneficial on eventual graft status [45].

Donor Management: General

Cardiovascular Performance and Monitoring

The etiology of low cardiac output in brain dead patients is complex and time dependent. It may be characterized by low preload due to vascular volume depletion, contractile

myocardial dysfunction, and variable SVR states ranging from extreme vasoconstriction from ICP-related sympathetic storm to vasodilation from sympathetic arrest. Resuscitation of the cardiopulmonary system benefits the function of all end organs in the brain dead donor. The variety of changes in volume status, cardiac inotropy, and peripheral vascular resistance that occur after brain death are similar to those in any pediatric critically ill patient with shock of diverse etiology. Intensivists should titrate cardiovascular therapy to clinical, biochemical and hemodynamic endpoints that ensure restoration of intravascular volume status, and appropriate support of the myocardium and vascular system to ensure optimal cardiac output for organ perfusion. Optimization with aggressive intensive care can optimize transplantation [59].

Evaluation of cardiocirculatory status is a global assessment of multiple variables. Traditional and vigilant hemodynamic assessments should be provided, based on physical findings, vital signs, central venous pressure, urine output, central or mixed venous oximetry and serial lactate measurements. Escalation of support should be accompanied by escalation of hemodynamic monitoring.

Echocardiographic parameters have also been demonstrated to be beneficial in predicting successful cardiac transplant outcomes [60, 61]. Echocardiographic systolic myocardial dysfunction is present in 42 % of adult brain death and associated with ventricular arrhythmias [60]. Diffuse wall motion abnormalities are a risk factor for 30-day heart transplant mortality [62]. Evaluation of left ventricular end diastolic diameter, ventricular wall thickness, and coronary flow are felt to influence transplantation [63]. Single echocardiographic evaluations may have limitations in detecting the reversible myocardial dysfunction often seen after brain injury [26]. Recent studies advocate pharmacologic stress evaluation for organ suitability [64]. The utility of serial echocardiograms to evaluate improvement in myocardial dysfunction in the brain dead donor and to better predict cardiac allograft survival has been reported in adults [65] and is evolving into routine practice. Studies show that serial echocardiogram lacked specificity but was particularly useful in showing improvements following aggressive donor management [66].

Right-sided pressures may underestimate left-sided pressures after brain death and may increase risk for elevated left-sided filling pressures and pulmonary edema [67]. Expert consensus supports pulmonary arterial catheterization (PAC) and cardiac output monitoring in adults, particularly if the donors are hemodynamically unstable or initial ejection fraction is less than 40–45 % [68, 69]. PAC and goal-directed hemodynamic therapy of initially unacceptable donors, in conjunction with hormonal therapy may improve the rate of organ procurement without compromising transplant outcomes [70]. A significant increase in heart recovery was seen with the use of PAC in adult studies [71]. The Transplantation Committee of the American College of Cardiology has recommended titrating volume infusions and

dopamine to thermodilution indices [72]. Justifications for PAC are not limited to the precise titration of hemodynamic support but are also required for the evaluation of suitability for heart and lung transplantation. As the use of PAC in PICU care is limited, serial echocardiography at q6-12 hourly intervals has been recommended [69].

Newer non-invasive methods of monitoring cardiac output are becoming more common because of their ease of use and safety, but are still not well validated for use in donor management, especially in children [73, 74]. Though management of the donor is similar to other shock states, monitoring of central venous saturations has not been recommended because of the lack of normal values in the donor patient [75]. Monitoring of other biochemical markers such as acidosis, lactates, and electrolytes is essential [76].

Hemodynamic Targets and Supports

Following the sympathetic storm, a subsequent reduction in catecholamines and sympathetic hormones result in a normotensive or hypotensive phase. This stage is characterized by impaired cardiac inotropy and chronotropy, impaired vascular tone and a reduced cardiac output. Clinical deterioration (progressive hypotension, hypoxia, anuria \pm cardiac arrest) during the interval from brain death to procurement is common without aggressive intervention [77]. Cardiovascular support should be based on rational physiology and should be preceded by volume resuscitation to normovolemia.

Preload

Significant volume depletion is anticipated in brain-injured patients after brain death due to fluid restriction, diuretics, hyperosmolar therapy, third space losses, hemorrhage and/or diabetes insipidus. In addition, a low SVR state may result in relative hypovolemia. In a Canadian study of 77 pediatric organ donors [2], 53 % suffered sustained hypotension and 35 % deteriorated to cardiac arrest. This was more common in patients treated with inotropic agents in the presence of a low central venous pressure and in those without anti-diuretic hormone replacement, emphasizing the importance adequate restoration of intravascular volume. Organ transplantation may be less favourable in preload dependent donors, possibly related to higher inflammatory response [78].

The optimal volume status of the brain dead patient is controversial and transplant-organ specific. Disparity exists between lung and kidney interests (“dry lungs” versus “wet kidneys”). In a study of crystalloid fluid management in 26 brain dead donors, a significant increase in the alveolar-arterial oxygen gradient was seen in those who achieved a central venous pressure (CVP) of 8–10 compared to those whose CVP was maintained at 4–6 mmHg [67]. Some authors advocate maintaining a CVP of 10–12 mmHg to volume replete those patients in whom only abdominal organs are to be procured, a CVP < 8 mmHg for potential

lung donors and a CVP of 8–10 mmHg if both thoracic and abdominal organs are to be harvested [79]. This approach is impractical since all organs should initially be considered potentially transplantable. Effectively, euolemia is the reasonable goal and the assessment of volume status should be based on experienced clinical evaluation [80–82].

Contractility

The preferred choice of contractility agents in PICU practice varies according to individual center. Traditionally, dopamine or dobutamine has been used as the initial inotrope of choice in the brain dead patient. However, no randomized trials exist comparing the hemodynamic effects of dopamine to other inotropes or vasopressors and their influence on graft survival. β -agonist therapy should be used with caution in potential heart donors given concerns about myocardial adenosine triphosphate (ATP) depletion and desensitization of β -receptors [83]. If the heart is being considered for donation, dopamine or its equivalent should not be escalated beyond 10 μ g/kg/min due to risks of increases oxygen demand [69]. High dose dopamine has been related to poor graft survival for hearts but favourable for other organs such kidneys [84, 85]. Use of epinephrine alone or as an adjunct may be appropriate in these cases.

Systemic Vascular Resistance

The functional sympathectomy associated with brain death results in low SVR that often requires the use of vasoconstricting agents. The concern over the use of alpha-agonists such as norepinephrine or phenylephrine has arisen because of the fear of inducing central and peripheral vasoconstriction and subsequent ischemia in coronary and vascular beds supplying potentially transplantable organs. However, in studies of other causes of shock states with low SVR (septic patients), norepinephrine, as compared to dopamine, was demonstrated to increase mean perfusion pressures without adverse effects to renal and splanchnic blood flow [86–88]. Early use of vasoconstrictor agents alone or in adjunction with inotropes is suggested [69].

Vasopressin and Catecholamine Sparing in Brain Death

Arginine vasopressin (AVP) is a unique agent because it can be used for a variety of applications in donor management, e.g. hemodynamic vasopressor support, diabetes insipidus therapy, and hormonal therapy. Brain death and hypotension are often associated with vasopressin deficiency [89]. Low-dose AVP infusions have been shown to improve hemodynamic stability and spare catecholamine use [89, 90]. Prolonged hemodynamic stability can be maintained after brain death with low-dose AVP (1–2 units/h), permitting a significant decrease in epinephrine and extended preservation of renal function [91]. In a rigorous, randomized study of volume-resuscitated brain dead organ donors supported with dopamine, 0.30 mU/kg/min infusion of AVP

significantly increased MAP and SVR and spared dopamine use compared to further fluid loading [92]. Pediatric donors given AVP (41 ± 69 mU/kg/h) respond by increasing MAP and weaning alpha-agonists (norepinephrine, epinephrine, phenylephrine) without significant differences in the quality of kidneys, livers and hearts recovered [21, 93]. Similar catecholamine-sparing effects of AVP have been demonstrated in septic shock patients with low SVR [94, 95].

Optimal dosing of AVP in relation to its effects on organ procurement and graft survival are unclear. Concern has been expressed regarding risks of splanchnic ischemia in vasodilatory shock [96, 97]. Practitioners should be cautioned regarding the multiple and confusing dosing units used throughout the literature. Although it is suggested that doses of AVP exceeding 0.04 U/min (approx. 40 mU/kg/h) may be associated with excessive vasoconstriction in sepsis [94] brain dead donors respond to AVP infusions of 0.04–0.1 U/min (40–100 mU/kg/h) [89] without histologic evidence of cardiac damage [98]. Recent evidence shows that systemic and SMA flow may be compromised with AVP versus dopamine [99]. Available literature suggests that the use of AVP at doses up to 0.04 U/min in adults (2.4 U/h) and 0.0003–0.0007 U/kg/min (0.3–0.7 mU/kg/min) in children can be recommended to support the MAP and spare catecholamines [69].

Oxygenation and Ventilation Strategies

Many potential donors have various etiologies of donor-related lung injury and dysfunction that may include neurogenic pulmonary edema, aspiration, atelectasis, pulmonary contusion, bronchopulmonary infection, alveolar-capillary inflammation, and diffuse alveolar damage [59]. Pulse oximetry, serial arterial blood gas monitoring, endotracheal tube suctioning, and serial chest x-rays are considered standard in donors [100]. Mechanical ventilation should be tailored to the following empirical recommendations: fraction of inspired oxygen (FiO_2) titrated to keep oxygen saturation $\geq 95\%$, partial pressure of arterial oxygen (PaO_2) ≥ 80 mmHg, pH 7.35–7.45, PaCO_2 35–45 mmHg, positive end expiratory pressure (PEEP) of 5 cm H_2O [69, 101, 102]. A prospective, randomized control trial in potential adult donors, ARDS-type lung protective strategies with tidal volumes of 6–8 mL/kg and 8–10 cmH $_2\text{O}$ PEEP significantly increased lung utilization for transplantation [103].

Metabolic and Endocrine

Glycemia and Nutrition

Hyperglycemia is common in brain dead donors [77]. It may be secondary to insulin resistance as pancreatic function appears to be preserved [104], which may be aggravated

by corticosteroid therapy and dextrose-based fluid replacements used for diabetes insipidus. Insulin is variably and inconsistently considered as part of hormonal resuscitation cocktails. The hypothesis that tight glycemic control in the brain dead donor improves graft survival has not been tested, but has been recommended by expert consensus [68, 69]. Hyperglycemia has been shown to be an independent risk factor for poor outcome after severe brain injury in children [105] and adults [106].

Dextrose infusions and nutrition are generally withheld in the acute PICU management after brain injury [107], a practice supported by animal models [108]. Malnutrition or depletion of cellular glycogen stores may be common during the phase of care leading to brain death [109]. The influence of donor nutrition on graft survival has been studied in several animal studies but not formally in humans. In a rabbit and porcine model, improved liver transplant survival was shown from donors receiving enteral nutrition versus fasting donors [110]. A significant improvement in hepatic sinusoidal lining cell viability has been demonstrated in rats with liver grafts from donors receiving enteral feeding and intraperitoneal glucose prior to liver procurement. Glycogen appears to protect the hepatic graft upon rewarming in rats [111].

The importance of nutritional support in the human multi-organ donor, however, is not clear but is of increased interest [112]. Studies of donor-specific predictors of graft function following liver transplantation suggested a length of stay in the ICU of greater than 3 days as a risk factor [113]. A contributing factor to this association may be the effect of starvation on the liver with depletion of glycogen stores. In a controlled prospective randomized study of 32 patients it was shown that an intraportal infusion of insulin (1 IU/kg/h) and glucose reglycogenates the liver, increases glycogen utilization during cold and rewarming periods, and improves transaminase levels [114]. However, the only human series of liver transplants that included donor nutritional status failed to identify an independent effect of donor nutrition on postoperative liver graft function [115]. As a general approach, intravenous dextrose infusions should be given routinely and routine enteral or parenteral feeding should be initiated or continued as tolerated [116].

Diabetes Insipidus and Hypernatremia

Dysfunction of the posterior pituitary in brain dead donors is common; anterior pituitary function is often preserved [117]. Histologic observations of the pituitary gland demonstrate various degrees of edema, hemorrhage, and tissue necrosis depending on the mechanism and site of traumatic or ischemic brain injury [118, 119]. This is likely to be a result of compromised blood supply to the cell bodies arising in the deep supraventricular and paraventricular nuclei of the hypothalamus, whose neurons supply the posterior pituitary and regulate AVP secretion. Anterior pituitary function is often preserved, implying that some blood supply via the

hypophyseal arteries, which arise extradurally, is reaching the median eminence of the hypothalamus [117]. Undetectable levels of antidiuretic hormone (ADH) have been noted in 75 % of brain dead donors, and diabetes insipidus is present in up to 87 % [29, 30, 54, 55]. Diabetes insipidus may commonly appear prior to the diagnosis of brain death [118] and is associated with hemodynamic instability and the compromise of transplantable organ function [2, 23, 77].

Hypernatremia is frequently encountered, resulting from the preceding hyperosmolar therapy for initial brain injury or poorly controlled diabetes insipidus. Donor hypernatremia > 155 mmol/L at procurement has been shown to be independently associated with hepatic and renal dysfunction or graft loss after transplantation [115, 120–122], although new evidence may show that these concerns may be less significant [123]. A prospective study demonstrated the benefit of correcting donor sodium (Na) \leq 155 mmol/L with equivalent graft success compared to donors who were never hypernatremic [124]. The mechanism of hepatic and kidney injury related to hypernatremia is unclear but may be related polyuria and dehydration and to the accumulation of idiogenic osmoles resulting in intracellular swelling after transplantation into the normonatremic recipient.

Ideal serum sodium (Na) target range is \geq 130 \leq 150 mmol/L [25]. A reasonable urine output target range is 0.5–3 ml/kg/h after brain death. Diabetes insipidus can be defined as a urine output > 4 ml/kg/h associated with rising serum Na \geq 145 mmol/L and serum osmolarity \geq 300 mosM and decreasing urine osmolarity \leq 200 mosM [69].

DDAVP (analog 1-desamino-8-D-arginine vasopressin, or desmopressin) is commonly used for the treatment of diabetes insipidus in brain death without adverse effect on early or late graft function after renal transplantation [125]. It is highly selective for the vasopressin V₂ receptor subtype found in the renal collecting duct and thus has a relatively pure antidiuretic effect with no significant vasopressor activity [126]. DDAVP has multiple potential routes of administration (iv, im, sc, intranasal, ETT) and corresponding variability of dose recommendations. In brain death, it is preferable to rely on the i.v. route with a recommended dosing range is 0.5–10 μ g iv every 6–8 h [127]. Given its lack of vasopressor action, it can be safely titrated to the effect of ablating polyuria and normalizing serum sodium. Improved organ yield is associated with DDAVP use in donor management [11, 128].

Many authors have advocated the use of AVP for the treatment of diabetes insipidus in organ donors to modulate both diabetes insipidus and support cardiovascular system [68, 69, 74, 93, 129, 130]. In pediatric case series, doses of vasopressin between 0.25 and 2.7 mU/kg/h have been used to successfully treat hypothalamic diabetes insipidus [131–134]. Doses between 0.5 and 15 U/h of AVP have been advocated in adults, though there are concerns about high doses causing coronary, renal and splanchnic vasoconstriction, potentially jeopardizing cardiac, renal, pancreatic and

hepatic function [99, 127]. The safety and efficacy of a combination of DDAVP (for its antidiuretic effect) with AVP as a vasopressor on cardiovascular and laboratory endpoints has been described [21, 92, 135]. Many protocols recommend separate dosing regimens for diabetes insipidus and support for perfusion. The upper limit of AVP recommended by the Transplantation Committee of the American College of Cardiology is 0.8–1.0 U/h (13–17 mU/kg/h) to treat diabetes insipidus [72].

Thyroid Hormone

Thyroid hormone increases cardiac output by improving both contractility and chronotropy, as well as by decreasing systemic vascular resistance [136]. The use of thyroid hormone therapy in brain dead donors is largely based on experimental animal models and human case series. Investigators describe variable levels of thyroid hormones after brain death and varying and conflicting effects of thyroid hormone administration. Thyroid-stimulating hormone (TSH), T₄ and T₃ levels were below normal in a majority of 22 brain dead donors [137]. Other studies have shown that these patients are suffering from “sick euthyroid syndrome” rather than TSH deficiency and do not require thyroid supplementation [54]. In the baboon model, T₃ levels become depleted after brain death and the resulting transition to anaerobic metabolism is reversed with T₃ replacement [138]. The positive effects on myocardial gene expression have been demonstrated [139].

In a comparative study in brain dead patients, T₃, cortisol and insulin promoted aerobic metabolism, reduced the need for inotropic support and improved the rate of cardiac graft procurement [140, 141]. Other investigators were unable to demonstrate any improvement in echocardiographic function or organ retrieval rates with a similar hormone regimen [142]. Serum free T₃ concentrations in organ donors may not correlate with hemodynamic stability [118] but replacement of thyroid hormone (T₃) has shown to reduce need for vasopressor support and may improve the likelihood of heart transplantations [143–146]. There is equipoise for routine use since many other studies did not show improvement in cardiac and hemodynamic status [147, 148].

T₄ infusion rather than T₃ does not reduce vasopressor requirements or especially in pediatric donors [21] but this may be related to impaired peripheral conversion to T₃. While there are numerous theoretical advantages of parenteral T₃ over T₄ (stability for iv infusion, does not require peripheral tissue conversion), it is extremely expensive in comparison to intravenous T₄ and may not be commercially available in many countries. In those UNOS patients receiving hormone therapy, T₄ was used in 93 % and T₃ in 6.9 % of cases, with insufficient numbers to discriminate any benefit of T₃ over T₄ [Rosendale, Kauffman, personal communication]. Most studies for thyroid replacement in the context of the organ donor are of low quality with poor study design, thus limiting objective analysis [149].

Corticosteroids

Several publications have advocated the use of high-dose methylprednisolone in an effort to diminish inflammation thought to be present in donor lungs [102, 130, 150] and other organs. The initial evidence for this was largely based on a single retrospective analysis of 118 consecutive lung donors administered a non-uniform protocol of methylprednisolone (mean 14.5 mg/kg) compared with 38 donors not receiving methylprednisolone and demonstrating a significant improvement in donor oxygenation and lung procurement rate [151]. A recent analysis of the California Donor Network database demonstrated an independent effect of methylprednisolone on the successful procurement of lungs from the donor [152]. The UNOS database showed that heart graft survival benefit was also found in those donors receiving corticosteroids alone [150]. Recent studies do reveal a highly proinflammatory environment in donors but do not actually show benefit from methylprednisolone replacement [20]. Although the optimal dose and time effect (if any) of corticosteroids in brain dead donors are uncertain, guidelines recommend methylprednisolone 15 mg/kg q24h [69].

Combined Hormonal Therapy

Despite conflicting literature regarding use of hormones individually, there is strong evidence supporting the use of combined hormonal therapy in organ donors, defined as vasopressin, thyroid hormone, and methylprednisolone (insulin is inconsistently included in this strategy). The United Network for Organ Sharing (UNOS) database shows a 46 % reduced odds of post-transplant death within 30 days and a 48 % reduced odds of early cardiac graft dysfunction with the use of combined hormonal therapy in a large retrospective cohort [150]. Benefit was also found in those donors receiving corticosteroids alone or in combination with T₃/T₄ which is supported by independent studies [153, 154]. Recovery of organs was most beneficial to heart and lung transplantation [155]. Analysis of UNOS data suggests a substantial benefit from hormone therapy with minimal risk. A multivariate logistic regression analysis of 18,726 brain dead donors showed significant increases in kidney, liver and heart utilization from donors receiving three-drug hormonal therapy. Significant improvements in 1-year kidney graft survival and heart transplant patient survival were also demonstrated [147, 148, 150]. More recently, however, in a prospective randomized study T₃ and methylprednisolone did not add to the effect on cardiac index shown by vasopressin and aggressive cardiovascular support [156]. Despite this recent finding, current expert consensus still strongly recommends the use of combined hormonal therapy for any donor with hemodynamic instability or reduced ejection fraction on echocardiography [68, 69].

Transfusion Thresholds

There are no rigorous studies that assess the role of red blood cell transfusions for short-term organ preservation during organ donor maintenance specifically. Prospective studies for transfusion thresholds suggest outcomes are similar with hemoglobin level at 7 g/dL in critically ill children [157]. However, consensus conferences recommend maintaining a hemoglobin level ≥ 10 g/dL or a hematocrit greater than 30 % [127, 130]. Large platelet transfusion requirements during liver transplant surgery are independently associated with more severe hepatic dysfunction after transplantation, but this is likely more indicative of a more technically complicated procedure and sicker recipient [115]. There is no literature identified to guide platelet or plasma factor replacement in the donor. Invasive procedures associated with bleeding risk may require correction of thrombocytopenia and coagulation status. Blood drawing for donor serology and tissue typing should occur prior to transfusions to minimize the risk of false results related to hemodilution. In regions where blood is routinely leukocyte depleted, and the risk of transmission of cytomegalovirus (CMV) is negligible and it may not be necessary to give CMV-negative blood to CMV-negative donors [69].

Invasive Bacterial Infections

Isolated cases of transmission of solid organ infection from donor to recipient may have significant consequences including graft infection, sepsis, and poor initial graft function [158–163]. While approximately 5 % of all donors will be bacteremic at the time of procurement, the routine use of broad spectrum antibiotics (vancomycin and ceftazidime/cefotaxime) in the recipient has been shown to prevent transmission of bacterial infection in organ recipients [164, 165]. Importantly, donor infections do not show differences in acute mortality or graft survival. The current expansion of potential marginal donors has increased the risk of infection. One study quoted bacteremia rates in the donor up to 21 % [166]. Donors with ICU stays greater than 3 days, rescue CPR, and inotropic agents are at increased risk [167]. Though rates of infections in donors may be up, organs obtained from donors with positive cultures continue to be transplanted safely, likely due to vigilant screening and polymicrobial therapy given to recipients [168, 169]. Other authors have described the successful transplantation of organs from donors declared brain dead from meningitis caused by *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Escherichia coli* without transmission to the recipient [170]. The finding of positive cultures does not preclude donation but may delay procurement until 24–48 h of treatment has been established. Prophylactic antibiotic therapy in the organ donor is generally not recommended.

Viral infections in the donor can affect recipients especially with post transplant immunosuppression. However, many chronic infections such as hepatitis B and C virus no longer preclude donation. Knowledge of potential risks is essential but often manageable in the appropriate recipient [171, 172].

Initial baseline blood, urine and endotracheal cultures should be obtained for all donors and repeated daily. PCR screens for common chronic viral infection are common. Positive blood cultures or presumed infections are not contraindications to organ donation but antibiotic therapy should be initiated early in cases of proven or presumed infection. Duration of therapy depends on the virulence of the organism and should be determined in consultation with the transplant team and infectious disease services.

Donor Management: Organ Specific

Heart

Wait list mortality among US children listed for heart transplant has decreased by two-thirds over the last 20 years [173]. Mostly this is related to extended donor and recipient criteria including ABO incompatible transplantation [174, 175]. This has not compromised clinical outcomes after transplantation [176]. Reasons for this are multifactorial but include improved donor management [177].

The majority of studies linking donor variables to heart transplant outcomes are in adults and related to known risk factors such as coronary artery disease, left ventricular hypertrophy, older age, diabetes mellitus, and chronic hypertension [62, 130, 178, 179]. While these variables may be indications for coronary angiography in the adult donor, they generally are not relevant to the pediatric population. Extrapolation from adult studies would suggest that myocardial dysfunction in the pediatric donor, as manifest by greater inotropic support [62, 180], pacemaker support [181], and reduced ejection fraction and/or wall motion abnormalities by echocardiography [62, 130] are important factors. Interestingly, donor CPR has not shown to be a negative factor for heart transplant survival [182, 183].

Potential heart donors should undergo routine screening by electrocardiogram (ECG) and 2D echocardiography. In children, initial echocardiography for heart donor evaluation should be performed only after hemodynamic resuscitation and repeat echocardiography should be considered after ≥ 6 h [69]. Intensive donor management has been shown to improve function on serial echocardiography and may improve transplantability in up to 50 % [66, 184, 185]. Some advocate that the majority of echographic abnormalities in donor hearts resolve in the transplant recipient prior to discharge [186]. Reduced function should not preclude consideration

for transplantation based on a single evaluation. Ejection fractions < 40 – 45 % do not necessarily translate into high transplant risk, as they may be related to inadequate cardiovascular resuscitation or neurogenic myocardial dysfunction that is reversible with time (see earlier sections). Adult data has shown significant improvements in echocardiographic function with time and conventional support [65], with up to 78 % of potential donors demonstrating clinically significant improvements [63, 184].

Serological markers such as donor troponin I and T have been linked to early cardiac graft failure [31, 187, 188] and should also be measured. However, these markers do not necessarily relate to graft dysfunction in recipients [189]. Though Tri-iodothyronine and methylprednisolone therapy is recommended, a recent study of 80 cardiac donors did not show acute improvement to cardiovascular function or donor yield [156].

Pulmonary artery catheterization (PAC) data has been linked to favorable transplant outcomes [70]. Reduced ejection fraction or hemodynamic instability has been recommended as an indication for PAC in adults to allow for both precision of hemodynamic support and evaluation of suitability for heart and lung transplantation especially in marginal donors [68, 190]. PAC use in pediatrics is still limited.

Lungs

Though lower yield than other organs donated, lung transplantation in pediatrics has increased with better techniques and improved management [191–193]. A relatively scarce donor pool has limited wider application for lung transplantation [194]. This has led to relaxation of donor criteria, specific donor management protocols that preserve lung function, and development of ex-vivo perfusion techniques to recondition suboptimal lungs, all of which have optimized transplantation [195, 196]. Outcomes for pediatric lung recipients are similar to adults but young children often do better due to a decreased incidence of rejection. Adolescent outcomes are poor mainly due to bronchiolitis obliterans [197].

The ‘ideal’ lung donor has been previously defined but significant advances have been made in donor and recipient management allowing for increased use of marginal or ‘extended criteria’ donors [198–200]. There is some evidence that organs transplanted using extended donor criteria may have higher rates of early graft rejection [201, 202]. The quality of the lung donor and the subsequent recipient outcomes are related to the possibility of this primary graft dysfunction which is a result of multifactorial hemodynamic, metabolic, and inflammatory insults resulting from the brain dead donor [203]. Primary pulmonary allograft failure has pathological features of acute lung injury (ALI) and occurs in 12–50 % of transplanted patients [204–206]. This is often

associated with inadequate lung preservation, ischemia-reperfusion injury and cellular rejection [207]. Despite this, many centers have adopted extended criteria in order to increase the number of potential donors [208, 209].

Traditional oxygenation criteria used as a threshold in the acceptance of donor lungs include a donor $\text{PaO}_2 > 300$ mmHg on FiO_2 of 100 % and PEEP of 5 cm H_2O (P/F ratio > 300) [210]. However, recent and evolving efforts have improved the current criteria for donor selection [191, 211]. Physiological, microbiological and histological evaluation of rejected lungs from the California transplant registry show 41 % of rejected lungs were judged suitable for transplantation based on pulmonary edema, intact alveolar fluid clearance, and histology [212]. In a case series of 15 brain dead adults, lung grafts that did not meet the usual criteria for transplantation were found to have higher dynamic and static elastance measurements than donor lungs that met standard transplantation criteria [213]. The outcomes of 49 marginal donors (i.e., failing to meet one or more of the ideal criteria) showed no significant difference in duration of post-transplant mechanical ventilation or P/F ratio compared to ideal donors [211]. Investigators have also challenged donor PaO_2 criteria by arguing that physiological donor factors influence peripheral arterial PaO_2 independent of isolated individual lung function [214]. Despite poor global oxygenation, parenchymal abnormalities isolated to one lung may not preclude procurement of the contralateral lung [215].

The cause of brain death does not correlate with lung transplant outcomes, but there is improved outcomes with longer time interval before retrieval suggesting longer and specific donor management may reduce lung injury over time [101, 216]. Pulse oximetry, serial arterial blood gas monitoring, endotracheal tube suctioning, rotational positioning, chest x-ray, bronchoscopy and bronchoalveolar lavage are considered standard in the lung specific care of donor [100]. Mechanical ventilation should be tailored to the general targets (see previous section) [103]. Similar to the management of lung injury in general, alveolar recruitment and pressure limited ventilation strategies should be used in potential donors [59]. New strategies for the improvement of lung function in the donor such as airway pressure release ventilation have been utilized [217]. Excessive fluid administration deteriorates alveolar-arterial oxygenation gradients in potential donors [67] and may be an indication for diuresis. Steroid administration may also reduce progressive lung water accumulation [101]. Prolonged ventilation in the supine position results in loss of alveolar expansion and microatelectasis. In an experimental rat model, donor lungs develop microatelectasis despite PEEP and a relatively short ventilatory period before organ procurement [218]. Prevention of alveolar collapse enhances post mortem preservation of pulmonary grafts in a rabbit model [219]. Recruitment maneuvers in the form of high sustained PEEP for short durations may be a useful adjunct to prevent alveolar stress and collapse [220]. Lung

donors failing traditional oxygenation criteria (P/F < 300) respond to aggressive bronchial toilet using bronchoscopy, physiotherapy, increasing tidal volume and increasing PEEP with improvements in P/F ratio > 300 . Lungs were subsequently transplanted without differences in ICU length of stay or 30-day mortality compared to recipients of ideal donors [221]. Hemodynamic and reperfusion injury seem to play a significant role in donor lung injury [222]. The early use of norepinephrine or vasopressin may reduce lung injury [223].

Recent guidelines suggest that there should be no pre-defined lower limit for the P/F ratio that precludes consideration for transplantation. Timing of evaluation, temporal changes, response to alveolar recruitment and recipient status should be considered [69]. In cases of unilateral lung injury, pulmonary venous partial pressure of oxygen during intraoperative assessment is required to reliably evaluate contralateral lung function.

Bronchoscopy and Bronchopulmonary Infections

The consensus of expert opinion supports the use of bronchoscopy for the purposes of examining the tracheobronchial tree for abnormalities and collecting microbiological specimens [68, 129, 211]. Pathological studies of lungs rejected for donation have indicated that bronchopneumonia, diffuse alveolar damage, and diffuse lung consolidation are the three most common reasons for being deemed unsuitable [214]. Between 76 % and 97 % of bronchoalveolar lavages (BAL) will grow at least one organism [224, 225]. The most commonly identified organisms included *Staphylococcus aureus* and *Enterobacter*, and in 43 % of transplants, similar organisms were isolated from recipient bronchoscopy. Pulmonary infection in the graft recipient results in significantly lower survival compared with recipients who do not develop early graft infection [226]. Recipients with donor BAL cultures positive for either gram positive or gram negative bacteria had longer mean mechanical ventilation times and inferior 6-month to 4-year survival than those with negative bacterial BAL cultures [227]. Trauma donors (versus intracerebral hemorrhage) may be at higher risk for aspiration and for intubation under less sterile field conditions and were generally ventilated longer [228]. The etiology of donor death is not associated with lung transplant mortality [204] but may influence the type of organisms found on BAL and subsequent graft infection risk. The high rates of positive bacterial and fungal BAL results suggest the need for more aggressive critical care management and antibiotic therapy [229].

Liver

Liver transplantation from deceased donors has become accepted as standard of care for many children with liver failure. Advances in donor and recipient management has optimized graft survival with 80–90 % 5 year survival rates

[230]. Whole liver transplants are still more successful with less morbidity and mortality than split liver grafts [231, 232]. Potential liver donors should be assessed by the following: aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin (direct and indirect where available), INR (or prothrombin time [PT]) (repeat q6h), serum electrolytes, creatinine, urea, Hepatitis B surface antigen (HBsAG), hepatitis B antibody (HBcAb), hepatitis C virus antibody positive (HCV Ab). There is no indication for routine liver imaging. The use of donor characteristics (donor risk index) and recipient matching using biochemical models in end stage liver disease (MELD) are becoming more useful in predicting liver transplant outcomes [233–235].

There is variation in organ quality and recipient outcomes; larger volume centers tend to use higher risk organs but also have higher disease severity resulting in worse outcomes [236]. Predictors of early graft dysfunction or failure for whole or split liver transplantation include donor history of cardiac arrest, older donor age in adult transplantation (>40 years), [113, 237, 238], very young age in pediatric transplantation [113], reduced size livers, moderate to severe steatosis on liver biopsy, prolonged cold ischemia time (>6 h) [121, 239, 240] and donor hypernatremia ($\text{Na} > 155 \text{ mmol/L}$). Donor hypernatremia is independently associated with death or retransplantation at 30 days [121] but this risk reverses with the correction of hypernatremia [124].

Although liver allograft dysfunction has been reported to be associated with prolonged ICU stay [113, 241], this was supported by univariate analysis but did not hold true by multivariate analysis [241]. In a cohort of 323 orthotopic liver transplants (OLT), longer donor hospitalization was not found to be associated with primary liver graft dysfunction [239]. Large platelet transfusion requirements during surgery are independently associated with more severe hepatic dysfunction after transplantation [115], although this may be indicative of a more technically complicated procedure, sicker recipient, or poor quality graft with subsequently greater sequestration of platelets within the donor liver [242]. As with other organs, the mechanisms of brain death itself impact the donor liver [243]. With the use of marginal livers for transplantation, studies are identifying more factors that may impact graft survival such as the liver's gross appearance, the donor P/F ratio, and the donor hemoglobin [244].

The sinusoidal lining cells (SLC) of the liver are particularly vulnerable to the effects of preservation-reperfusion injury, the extent of which depends on the duration of cold ischemia rather than reperfusion. Cold preservation causes the SLC to become edematous and detach into the sinusoidal lumen [245]. While some authors recommend routine donor liver biopsies in all liver donors in an effort to decrease the rate of early graft dysfunction or failure [246, 247], the use of a biopsy in the decision making of liver suitability has generally been restricted to evaluating the amount of steatosis or in the presence of active hepatitis C in the appropriate risk groups.

Kidney

Donor age ≥ 40 or ≤ 10 years were thought to be independently associated with risk for graft failure [248, 249]. Now, recipients of kidneys from young donors < 5 years old have equivalent patient and graft survival [250]. En bloc kidneys from pediatric donors now show comparable outcomes with living kidney donation [251]. Older kidneys have a higher incidence of renovascular or parenchymal injury [249]. Adult donor characteristics that are independently associated with graft failure risk include creatinine $> 133 \mu\text{mol/L}$, history of hypertension independent of duration and cerebrovascular accident (CVA) as the cause of donor death [248]. During the past few years, there has been a renewed interest in the use of expanded criteria donors for kidney transplantation to increase number of donations with improving outcomes [252]. However, these kidneys have worse long-term survival and are only recommended for older recipients [253, 254].

A normal creatinine clearance ($>80 \text{ ml/min/1.73 m}^2$), as estimated by the Schwartz formula [255], defines the optimal function threshold for transplantation. However, an abnormal serum creatinine or calculated creatinine clearance in a donor does not necessarily preclude use of the kidneys [256]. Urinalysis is essential to rule out kidney abnormalities and serum creatinine and serum urea (blood urea nitrogen) measurements should be obtained q6h. Ultrasound with Doppler flow of renal vessels is often requested if creatinine levels are abnormal. If contrast angiography is performed (e.g. cerebral, coronary) N-acetylcysteine with hydration should be administered both before and after the angiographic procedure in order to reduce the risk of contrast nephropathy [257] in potential donors, particularly in those with reduced renal function.

Delayed graft function predicts the development of adverse events such as decreased graft survival, decreased recipient survival and increased allograft nephropathy [258]. Most studies do not link a specific cause of brain death as a predictor of graft function in children [259]. The brain death process itself can affect acute rejection in renal transplantation [260, 261]. Greater sympathetic activity during the process produces endothelial damage, complement activation, and a proinflammatory state increases organ immunogenicity, then promoting rejection after transplant [262, 263]. Targeting this inflammatory state may improve outcomes of recipients [264, 265].

Other donor risk factors predicting kidney allograft dysfunction include hemodynamics, age, last creatinine level prior to donation, and cold ischemic time [266]. Donor hemodynamic instability is correlated with post-transplant acute tubular necrosis in adults [77, 267, 268] and children [2]. Reduced graft survival or acute tubular necrosis may occur in organs retrieved from donors receiving high-dose dopamine ($>10 \mu\text{g/kg/min}$) but these effects may be limited to donors who are hypotensive at the time of organ retrieval

[268]. Hemodynamic resuscitation may improve outcome as donor use of dopamine and/or noradrenaline is independently associated with a lower risk of acute rejection [269], lower rate of delayed graft function [84, 270], and reduces the need for recipient dialysis [271]. In adults, donor hypertension is also a risk factor for inferior outcomes [272]. It is suggested that the time taken to optimize donor cardiovascular status may reduce renal ischemic injury and optimize donor yield [273, 274].

In an analysis of the Collaborative Transplant Study database of kidney transplants, cold ischemic preservation time > 12 h resulted in progressively worsening recipient graft survival, particularly once the cold ischemia time (CIT) was ≥ 48 h [275]. Other analyses have suggested that CIT is predictive of poorer graft survival [248] or function [267] if it was >24 h. Preservation incorporating pulsatile perfusion, rather than cold storage, may reduce the incidence of delayed graft function [276, 277].

Intestine

Small bowel transplantation has become an increasingly feasible option for short bowel syndrome and liver failure [278]. Long term survival following intestinal transplant is above 60 %, but the incidence of morbidity and mortality is still significant [279, 280]. Because of this, many feel that intestinal transplantation as an option is still premature and remains unique to specialized centres only [281, 282]. For the brain dead donor, non-absorbable antibiotics for selective bowel decontamination are sometimes used for liver and intestine transplantation to prevent postoperative infections. Results are best if given >3 days prior to transplantation [283]. A meta-analysis showed an 84 % relative risk reduction in the incidence of gram negative infection following liver transplantation; however, the risk of antimicrobial resistance should be considered [284]. More recent studies have not duplicated these results. At this time, selective bowel decontamination is not routinely administered [285].

Logistics of Organ Donation

Donor Management Protocols and Education

One of the main reasons for insufficient organ procurement has been low organ yield due to poor multiorgan failure management in the potential donor [82]. Evidence has shown that multidisciplinary donor management protocols can improve donation outcomes [286, 287]. When these strategies are used, there are a significantly improved number of organs transplanted per donor [3, 4]. This is mostly

attributed to the improvement in basic cardiovascular and respiratory monitoring and treatment [288–290]. Improved multimodal strategies aimed at preserving organ function specifically may increase numbers of potential donors, especially with the increasing use of “marginal” donors [81]. These protocols need to be supported with appropriate medical and nursing education [291–293] and influencing attitudinal changes for the role of donor [294]. Policies for organ donation and management should be developed with aim to change the culture at the bedside and with hospital administration [295, 296].

Optimal Time of Organ Procurement

In general, after brain death has been declared and consent to organ donation has been granted, all efforts are made to complete logistics and initiate procurement as quickly as possible. Expediting the interval from brain death to surgical procurement may allow grieving families to leave the hospital sooner and reduce ICU length of stay. This approach may also have been influenced by the misperception that brain dead patients are irretrievably unstable [77].

As a concept fundamental to ICU multiorgan support, resuscitation of the cardiopulmonary system benefits all end organs. Neurogenic myocardial injury related to primary brain injury is largely reversible with time and treatment [30, 65, 184]. Australian investigators advocate a delay in organ procurement until marginal donor lungs have been optimized with aggressive bronchial toilet using bronchoscopy, physiotherapy, increasing tidal volume and increasing (PEEP) [152, 221]. In a large cohort study of 1,106 renal transplant recipients, longer duration of brain death (time from declaration of brain death to onset of cold ischemia) was associated with improved initial graft function and graft survival, suggesting that the time taken to optimize donor cardiovascular status may reduce ischemic injury [273]. Despite early reports to the contrary [113], liver allograft dysfunction is not associated with prolonged ICU stay by multivariate analysis [239, 241]. A period of time may be needed to determine the trend of elevated AST or ALT, as generally accepted upper limits may be exceeded if the levels are falling rapidly (e.g., following a hypotensive episode with resuscitation).

Temporal changes in multi-organ function after brain death demand flexibility in identifying the optimal time of procurement. Recent consensus guidelines stress the importance of taking the necessary time in the ICU to optimize multi-organ function for the purposes of improving organ utilization and transplant outcomes [69]. Reversible organ dysfunction can be improved with resuscitation and re-evaluation and may include:

- Myocardial/cardiovascular dysfunction
- Oxygenation impairment related to potentially reversible lung injury
- Invasive bacterial infections
- Hyponatremia
- The need to evaluate temporal trends in aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
- The need to evaluate temporal trends in creatinine
- Any other potentially treatable situation.

This treatment period may be extended 24–48 or longer and should be accompanied by frequent re-evaluation to demonstrate improvement in organ function toward defined targets. Extending the interval of donor care in the ICU to optimize transplant outcomes should be factored into donation consent discussions and should be consistent with the wishes of the family or surrogate decision maker. Adequate PICU resource allocation should be anticipated.

Decisions Regarding Transplantability

End-of-life care in the ICU includes all efforts to actualize the opportunity and expressed intent to donate organs. Given the management of brain death and the organ donor is the exclusive domain of ICU practice, it is incumbent on critical care practitioners to assume leadership in this regard, in collaboration with organ procurement agencies and transplant programs. Table 38.3 provides an example of standing orders for pediatric donors to help guide practice [69].

It is important for ICU staff to know that individual programs may have different function thresholds for accepting organs, dependent on program experience and urgency of recipient need. Although the non-utilization of organs is most commonly related to organ dysfunction, it is also related to donor characteristics and/or flaws in the processes of transplant evaluation and decision making. A four-center Canadian review of heart and lung utilization identified deficits in the consent to individual organs, the offering of organs, and the utilization of offered organs unrelated to organ dysfunction [297]. Consent should be requested for all organs regardless of baseline function and all organs should be offered. Ideally, final decisions about transplantability should rest with the individual transplant programs represented by the organ-specific transplant doctors.

Management of marginal organs should include resuscitation and reevaluation to allow for potential organ rescue and utilization. Transplant programs should be accountable to the donor family and ICU donation efforts for the non-utilization of organs, to ensure that all useable organs are used. This evolving collaboration to establish best donor management practices in the ICU must be linked to ensuring optimal organ utilization, which in turn, must be linked to transplant graft and patient outcomes.

Table 38.3 Standing orders for organ donor management: pediatrics

Standard monitoring

1. Urine catheter to straight drainage, strict intake and output
2. Nasogastric tube to straight drainage
3. Vital signs q1h
4. Pulse oximetry, 3-lead electrocardiogram (EKG)
5. Central venous pressure (CVP) monitoring
6. Arterial line pressure monitoring

Laboratory investigations

1. Arterial blood gas (ABG), electrolytes, glucose q4h and PRN
2. CBC q8h
3. Blood urea nitrogen (BUN), creatinine q6h
4. Urine analysis
5. AST, ALT, bilirubin (total and direct), international normalized ratio (INR) (or prothrombin time [PT]), partial thromboplastin time (PTT) q6h

Hemodynamic monitoring and therapy

General targets: age-related norms for pulse and blood pressure (BP)

1. Fluid resuscitation to maintain normovolemia, CVP 6–10 mmHg
2. Age-related treatment thresholds for arterial hypertension:

Newborns–3 months	>90/60
>3 m–1 year	>110/70
>1 year–12 year	>130/80
>12 year–18 year	>140/90

 - a. Wean inotropes and vasopressors, and, if necessary
 - b. Start

Nitroprusside 0.5–5.0 µg/kg/min, or
Esmolol 100–500 µg/kg bolus followed by 100–300 µg/kg/min
3. Serum lactate q2–4h
4. Central venous oximetry q2–4h; titrate therapy to central SVO₂ ≥ 60 %

Agents for hemodynamic support

1. Dopamine 1–10 µg/kg/min
2. Vasopressin 0.0003–0.0007 U/kg/min (0.3–0.7 mU/kg/min) to a maximum dose of 2.4 U/h
3. Norepinephrine, epinephrine, phenylephrine (caution with doses > 0.2 µg/kg/min)

Glycemia and nutrition

1. Routine intravenous (iv) dextrose infusions
2. Continue enteral feeding as tolerated
3. Continue parenteral nutrition if already initiated
4. Initiate and titrate insulin infusion to maintain serum glucose 6–10 mmol/L

Fluid and electrolytes

Targets:

1. Urine output 0.5–3 ml/kg/h
2. Serum sodium (Na) ≥ 130 ≤ 150 mM
3. Normal ranges for potassium, calcium, magnesium, phosphate

Diabetes insipidus

Defined as:

1. Urine output > 4 ml/kg/h, associated with:
 - a. Rising serum Na ≥ 145 mmol/L and/or
 - b. Rising serum osmolality ≥ 300 mosM and/or
 - c. Decreasing urine osmolality ≤ 200 mosM

(continued)

Table 38.3 (continued)

Diabetes insipidus therapy

1. Titrate therapy to urine output ≤ 3 ml/kg/h
 - a. iv vasopressin infusion 0.0003–0.0007 U/kg/min (0.3–0.7 mU/kg/min) to a maximum dose of 2.4 U/h, and/or
 - b. Intermittent 1-desamino-D-arginine vasopressin (DDAVP) 0.25–10 μ g iv q6h

Combined hormonal therapy

Defined as:

1. Tetra-iodothyronine (T_4) 20 μ g iv bolus followed by 10 μ g/h iv infusion (or 50–100 μ g iv bolus followed by 25–50 μ g iv bolus q12h)
2. Vasopressin 0.0003–0.0007 U/kg/min (0.3–0.7 mU/kg/min) to a maximum dose of 2.4 U/h
3. Methylprednisolone 15 mg/kg (≤ 1 g) iv q24h

Indications:

1. 2D echocardiographic ejection fraction ≤ 40 %, or
2. Hemodynamic instability (includes shock unresponsive to restoration of normovolemia and requiring vasoactive support [dopamine >10 μ g/min or any other vasopressor agent])
3. Consideration should be given to its use in all donors

Hematology

1. Hemoglobin (Hgb) optimal ≥ 100 g/L for unstable donors, lowest acceptable ≥ 70 g/L
2. Platelets, INR, PTT no predefined targets, transfuse in cases of clinically relevant bleeding
3. No special transfusion requirements

Microbiology (baseline, Q24h and PRN)

1. Daily blood cultures
2. Daily urine cultures
3. Daily endotracheal tube (ETT) cultures
4. Antibiotics for presumed or proven infection

Heart Specific

1. 12-lead EKG
2. Troponin I or T, q12h
3. 2D echocardiography
 - a. Should only be performed after fluid and hemodynamic resuscitation
 - b. If 2D echo ejection fraction ≤ 40 % then repeat echocardiography at q6–12 h intervals

Lung specific

1. Chest x-ray q24h and PRN
2. Bronchoscopy and bronchial wash gram stain and culture
3. Routine ETT suctioning, rotation to lateral position q2h
4. Mechanical ventilation targets:
 - a. Tidal volume (V_t) 8–10 ml/kg, positive end expiratory pressure (PEEP) 5 cm H_2O , peak inspiratory pressure (PIP) ≤ 30 cm H_2O
 - b. pH 7.35–7.45, partial pressure of arterial carbon dioxide ($PaCO_2$) 35–45 mmHg, partial pressure of arterial oxygen (PaO_2) ≥ 80 mmHg, oxygen (O_2) sat ≥ 95 %
5. Recruitment maneuvers for oxygenation impairment may include:
 - a. Periodic increases in PEEP up to 15 cm H_2O
 - b. Sustained inflations (PIP @ 30 cm H_2O \times 30–60 s)
 - c. Diuresis to normovolemia

[Based on data from ref. 69]

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