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Review Article

Optimisation of the organ donor and effects on transplanted organs: a narrative review on current practice and future directions

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Summary

Mortality remains high for patients on the waiting list for organ transplantation. A marked imbalance between the number of available organs and recipients that need to be transplanted persists. Organs from deceased donors are often declined due to perceived and actual suboptimal quality. Adequate donor management offers an opportunity to reduce organ injury and maximise the number of organs than can be offered in order to respect the donor's altruistic gift. The cornerstones of management include: correction of hypovolaemia; maintenance of organ perfusion; prompt treatment of diabetes insipidus; corticosteroid therapy; and lung protective ventilation. The interventions used to deliver these goals are largely based on pathophysiological rationale or extrapolations from general critical care patients. There is currently insufficient high-quality evidence that has assessed whether any interventions in the donor after brain death may actually improve immediate post-transplant function and long-term graft survival or recipient survival after transplantation. Improvements in our understanding of the underlying mechanisms following brain death, in particular the role of immunological and metabolic changes in donors, offer promising future therapeutic opportunities to increase organ utilisation. Establishing a UK donor management research programme involves consideration of ethical, logistical and legal issues that will benefit transplanted patients while respecting the wishes of donors and their families.

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Introduction

Organ transplantation has become the clinical and cost-effective treatment of choice for end-stage organ failure [1]. However, there continues to be an imbalance between the number of organs donated and potential recipients on the waiting list. This is despite many efforts to increase donation and organ utilisation, including better strategies to retrieve and preserve organs as well as improve

immunosuppression or reduce complications after transplantation. Although this imbalance remains, mortality for those who remain on the transplant waiting list continues to be high. In the past decade, animal and preclinical research has concentrated on increasing our understanding of relevant mechanisms contributing to poor post-transplant organ quality, chronic rejection and loss of graft function. There has been little emphasis on risk factors in the donor and the role of donor management before organ retrieval.

Cerebral injury due to haemorrhage, trauma or other causes of anoxia is the common diagnosis in potential organ donors. It has been shown to be associated with significant haemodynamic, metabolic and hormonal changes. These result in a progressive and profound systemic inflammatory response, affecting function and viability of donor organs before retrieval and transplantation. The period of donor management, after confirmation of death by neurological criteria and before organ retrieval is carried out, may therefore offer an important opportunity to reduce organ injury and potentially initiate repair and regeneration. In the UK, a donor optimisation care bundle has been developed to unify clinical practice across the country [2]. However, the majority of the protocol is based on our current understanding of pathophysiology in the donor and the limited evidence derived predominantly from studies powered to physiological endpoints and/or short-term outcomes [1], rather than long-term patient-centred recipient outcomes [3].

The aims of this review are to provide a critical overview of the currently available treatments or interventions used during donor management to facilitate and underpin donation after brain death (DBD); to explore future therapeutic options considering available animal and preclinical research; and to discuss the challenges and ethical frameworks for conducting clinical studies in this context.

Methods

We searched MEDLINE, PubMed, the Cochrane Central Register of Controlled Trials, Embase and Google Scholar to identify clinical trials of interventions during organ donor management. Titles and abstracts were screened and references of all identified systematic reviews, randomised controlled trial, observational studies, review articles and current treatment guidelines were checked for further relevant literature. The search was restricted to literature from 1980 to 2019, but older important publications were not excluded. Topics beyond the scope of this review were referenced by relevant narrative reviews, systematic reviews or clinical guidelines, where applicable. A snowballing principle was used to identify relevant preclinical and animal studies. The literature searches included the following terms: organ donor or deceased donor or brain dead donor or heart-beating donor, donation after death or DBD or donation after neurological death or deceased donation or organ donation, tissue and organ procurement, (pre-) treatment or management or (pre-)intervention, (neuro-) intensive care or (neuro-) critical care.

Donor optimisation

Physiological optimisation of the potential donor after brain death

Donor optimisation is an essential active process in organ donation that switches the focus from treatments that are directed towards recovery of the injured brain to those that are focused on the cardiopulmonary and metabolic resuscitation of potentially transplantable solid organs, after the diagnosis of death by neurological criteria. This process should be initiated as soon as possible following consent (or authorisation in Scotland) for organ retrieval. The immediate objectives of donor optimisation, which we will discuss in detail, include:

1. correction of hypovolaemia
2. commencement of vasopressin and weaning of catecholamine infusions
3. prompt diagnosis and management of diabetes insipidus
4. high-dose methylprednisolone (15 $mg.kg^{-1}$), to attenuate the effects of the inflammatory response
5. application of lung protective, 'low-stretch', ventilation strategies (tidal volume 4–8 $ml.kg^{-1}$ ideal body weight, plateau pressure < 30 cmH_2O, PEEP 5–10 cmH_2O) and recruitment manoeuvres.

It is important to note that to date in-depth studies to assess the effect of donor management on the outcome after organ transplantation are lacking. There is currently insufficient high-quality evidence to conclude that any intervention in the potential DBD donor improves immediate function, long-term graft survival or recipient survival after transplantation [3]. A summary of the key studies informing the evidence base for donor management interventions is provided in Table 1.

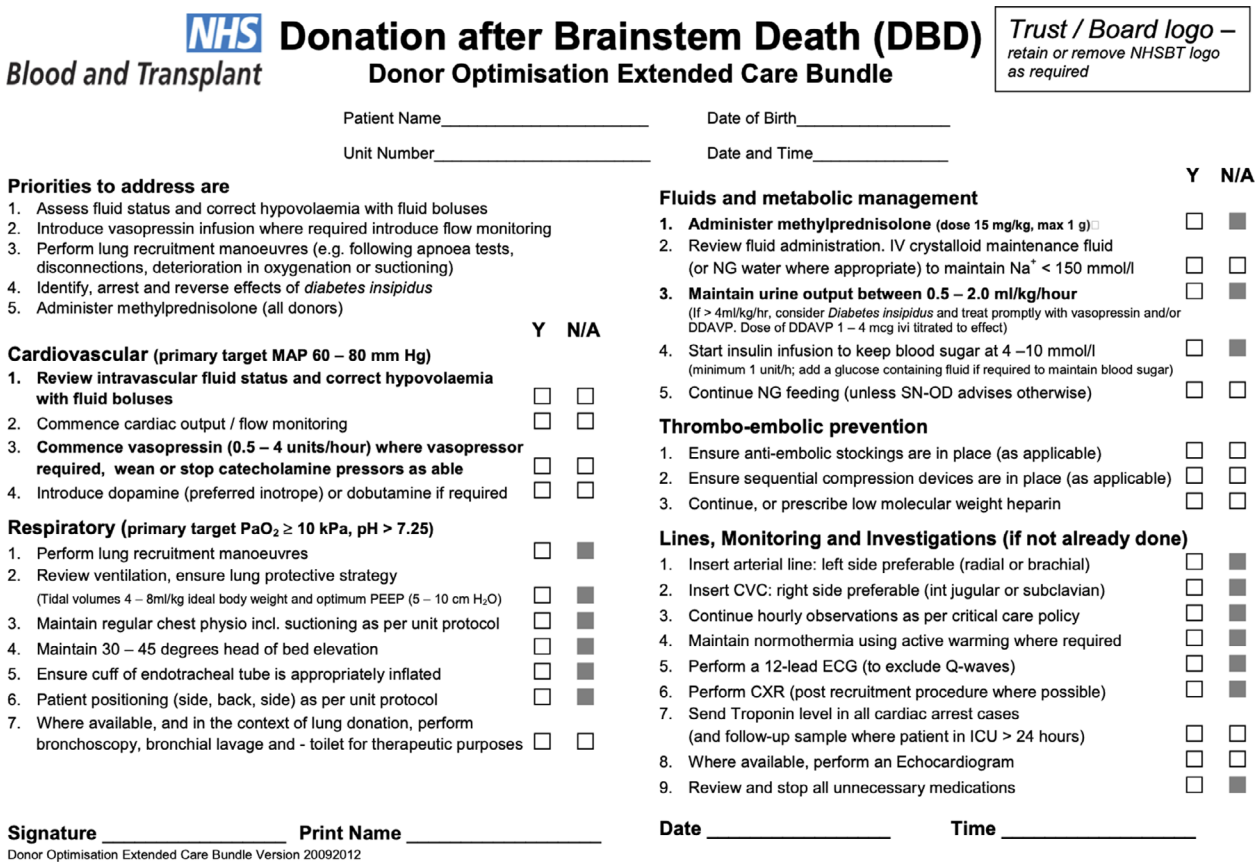
Cardiovascular management

The catecholamine 'storm' caused by cerebral injury leading to brainstem compression initially results in an increase in arterial blood pressure, afterload, left atrial pressure and pulmonary hydrostatic pressure [4, 5]. Central redistribution of blood volume occurs along with

Table 1 Characteristics of key studies informing evidence base of donor optimisation interventions.

Intervention	Study	Study type	Number of donors randomly assigned	Comparator	Primary outcome(s)	Key finding
Protocol-guided fluid therapy targeting cardiac index, mean arterial pressure and pulse pressure variation	Al-Khafaji et al. [14]	Multicentre RCT, USA	556	Usual care	Number of organs transplanted per donor	Protocol-guided fluid therapy does not increase the number of organs transplanted per donor when compared with usual care
Dopamine 4 $\mu g.kg^{-1}.min^{-1}$, initiated after consent and until cross clamping	Schnuelle et al. [20]	Multicentre RCT, Germany	264	No treatment	Dialysis requirement in recipients during first week after transplantation	Dopamine treatment resulted in fewer patients requiring multiple dialysis sessions when compared with no dopamine
Desmopressin 1 µg bolus every 2 h when urine output > 300 $ml.h^{-1}$	Guesde et al. [32]	Single-centre RCT, France	97	No desmopressin	Early renal function (serum creatinine, haemodialysis requirements) in first 15 days post-transplantation	No difference in early renal function between both study groups. Lower cumulative diuresis in desmopressin group
Corticosteroids (methylprednisolone)	D'Aragon et al. [39]	Systematic review	682	Usual care or placebo	Vasopressor requirement in donors; organ recovery from donors; recipient graft rejection; and adverse effects	No individual study or pooled analysis showed benefit of corticosteroids for any outcome
Thyroid hormone replacement	Macdonald et al. [54]	Systematic review	209	Placebo	Donor cardiac index	Thyroid hormone replacement therapy has no effect on donor cardiac index; however, included trials included very small numbers of donors with haemodynamic instability
Lung protective ventilation	Mascia et al. [49]	Multicentre RCT, Europe	118	Conventional ventilation	Number of organs donors meeting eligibility criteria for lung retrieval	Lung protective ventilation increases the number of potentially eligible donors and retrieved lungs compared with a conventional strategy
Mild hypothermia (34 °C–35 °C)	Niemann et al. [57]	Multicentre RCT, USA	394	Normothermia (36.5 °C–37.5 °C)	Delayed graft function in kidney transplant recipients	Mild donor hypothermia significantly reduced the rate of delayed graft function among recipients when compared with normothermia)

i.v., intravenous; PEEP, positive end expiratory pressure; RCT, randomised controlled trial.



NHS Blood and Transplant

Donation after Brainstem Death (DBD)

Donor Optimisation Extended Care Bundle

Trust / Board logo – retain or remove NHSBT logo as required

Patient Name_____ Date of Birth_____

Unit Number_____ Date and Time_____

Priorities to address are

1. Assess fluid status and correct hypovolaemia with fluid boluses
2. Introduce vasopressin infusion where required introduce flow monitoring
3. Perform lung recruitment manoeuvres (e.g. following apnoea tests, disconnections, deterioration in oxygenation or suctioning)
4. Identify, arrest and reverse effects of *diabetes insipidus*
5. Administer methylprednisolone (all donors)

	Y	N/A
Cardiovascular (primary target MAP 60 – 80 mm Hg)		
1. **Review intravascular fluid status and correct hypovolaemia with fluid boluses**	☐	☐
2. Commence cardiac output / flow monitoring	☐	☐
3. **Commence vasopressin (0.5 – 4 units/hour) where vasopressor required, wean or stop catecholamine pressors as able**	☐	☐
4. Introduce dopamine (preferred inotrope) or dobutamine if required	☐	☐
Respiratory (primary target $PaO_2 \geq 10$ kPa, pH > 7.25)		
1. Perform lung recruitment manoeuvres	☐	■
2. Review ventilation, ensure lung protective strategy (Tidal volumes 4 – 8ml/kg ideal body weight and optimum PEEP (5 – 10 cm H_2O)	☐	■
3. Maintain regular chest physio incl. suctioning as per unit protocol	☐	■
4. Maintain 30 – 45 degrees head of bed elevation	☐	■
5. Ensure cuff of endotracheal tube is appropriately inflated	☐	■
6. Patient positioning (side, back, side) as per unit protocol	☐	■
7. Where available, and in the context of lung donation, perform bronchoscopy, bronchial lavage and - toilet for therapeutic purposes	☐	☐

	Y	N/A
Fluids and metabolic management		
1. **Administer methylprednisolone (dose 15 mg/kg, max 1 g)**	☐	■
2. Review fluid administration. IV crystalloid maintenance fluid (or NG water where appropriate) to maintain $Na^+ < 150$ mmol/l	☐	☐
3. **Maintain urine output between 0.5 – 2.0 ml/kg/hour** (If > 4ml/kg/hr, consider *Diabetes insipidus* and treat promptly with vasopressin and/or DDAVP. Dose of DDAVP 1 – 4 mcg ivi titrated to effect)	☐	■
4. Start insulin infusion to keep blood sugar at 4 –10 mmol/l (minimum 1 unit/h; add a glucose containing fluid if required to maintain blood sugar)	☐	■
5. Continue NG feeding (unless SN-OD advises otherwise)	☐	☐
Thrombo-embolic prevention		
1. Ensure anti-embolic stockings are in place (as applicable)	☐	☐
2. Ensure sequential compression devices are in place (as applicable)	☐	☐
3. Continue, or prescribe low molecular weight heparin	☐	☐
Lines, Monitoring and Investigations (if not already done)		
1. Insert arterial line: left side preferable (radial or brachial)	☐	■
2. Insert CVC: right side preferable (int jugular or subclavian)	☐	■
3. Continue hourly observations as per critical care policy	☐	■
4. Maintain normothermia using active warming where required	☐	■
5. Perform a 12-lead ECG (to exclude Q-waves)	☐	■
6. Perform CXR (post recruitment procedure where possible)	☐	■
7. Send Troponin level in all cardiac arrest cases (and follow-up sample where patient in ICU > 24 hours)	☐	☐
8. Where available, perform an Echocardiogram	☐	☐
9. Review and stop all unnecessary medications	☐	■

Signature _____ **Print Name** _____

Date _____ **Time** _____

Donor Optimisation Extended Care Bundle Version 20092012

Figure 1 Donor optimisation extended care bundle for donation after brain stem death, http://odt.nhs.uk/pdf/dbd_care_bundle.pdf

pulmonary and splanchnic vasoconstriction and endothelial damage. Myocardial injury has been reported to occur in approximately 40–50% of potential DBD donors [6, 7]. Attenuating this response may improve the availability of the heart for transplantation but high-quality data are lacking [8]. A recent efficacy trial of donor simvastatin treatment in heart transplantation found significantly lower levels of plasma troponin T and I and N-terminal pro-B-type natriuretic peptide in recipients who received hearts from donors treated with simvastatin compared without simvastatin [8]. These preliminary data require further testing in large, well-designed randomised trials [9].

After brainstem infarction, loss of sympathetic tone frequently leads to profound vasoplegia and hypotension, which if left untreated, can lead to global hypoperfusion of all solid organs. Therefore, the primary goal of haemodynamic management is to maintain organ perfusion through judicious use of intravenous fluids and vasopressors, aiming for the targets shown in Fig. 1. These targets are largely derived from observational studies, case series, expert opinion or extrapolated from management of organ failure in other critically ill patients. The ideal fluid resuscitation strategy is yet to be determined as different approaches are likely to be beneficial for different organs. Euvolaemia is often described as the target but this remains an ill-defined concept. Traditionally, aggressive/liberal fluid resuscitation was believed to be beneficial for kidney donation whereas conservative/restrictive approaches benefitted lung donation. Available evidence from cohort studies suggests that although excessive fluid administration is likely to be detrimental to potentially transplantable lungs [10, 11], a lung-targeted management strategy has no adverse effect on kidney graft survival [12]. These findings are in keeping with much larger studies undertaken in patients with acute respiratory distress syndrome, which showed that prioritising lung function did not cause acute kidney injury [13].

As there is little consensus regarding haemodynamic monitoring, using the same monitors to guide management of haemodynamic shock as used in critically ill patients seems reasonable (e.g. invasive arterial line monitoring and markers of perfusion including serum lactate, urine output and venous oxygen saturation). Additional measurements gained using echocardiography and bed-side cardiac

output monitoring (e.g. oesophageal Doppler and pulse contour analysis) may also be used where available, but these have not been shown to be superior to conventional therapy in increasing the number of transplanted organs per donor [14].

Volume resuscitation with isotonic crystalloids, either with 0.9% saline or Ringer's lactate solution, is recommended [15]. Hydroxyethyl starches containing large-sized molecules should be avoided due to their recognised adverse effects such as acute kidney injury and coagulopathy in critically ill patients [16], but also due to a reported 41% increase in the risk of delayed graft failure following kidney transplantation [17].

Use of vaso-active agents

Dopamine has traditionally been the first-line vaso-active agent of choice due to its inotropic, vasopressor and immunomodulatory effects, but there are insufficient high-quality data to recommend its use over other agents [18]. Noradrenaline, with potent α-agonist effects, may increase pulmonary capillary permeability and cardiac afterload, whilst also potentiating coronary and mesenteric ischaemia but is often required. A small trial, involving 27 DBD donors, found an association between poor right ventricular function and noradrenaline use, which in turn was associated with worse cardiac function and increased mortality at 1 year [19]. Schnuelle et al. randomly assigned 264 DBD donors to receive low-dose dopamine ($4\ \mu g.kg^{-1}.min^{-1}$) or placebo, and found that donor pre-treatment with dopamine reduced the need for dialysis in recipients after kidney transplantation [20]. However, 5-year graft survival did not differ between control and treatment arms [21]. A post-hoc regression analysis demonstrated that longer durations of dopamine administration reduced dialysis need and graft failure, with maximal increase in efficacy occurring at 7 hours of administration for both outcomes [21]. This finding requires prospective validation. It should be noted that although there is a recognised specific pathophysiology of vasoplegia in the potential donor as described above, meta-analyses have not found any benefit of dopamine in preventing or mitigating acute kidney injury in other vasoplegic or shock states in other critically ill patients [22, 23].

Vasopressin has theoretical advantages and is now increasingly being used as first-line therapy to achieve haemodynamic goals. Vasopressin binds to G-protein-coupled V1 receptors on peripheral vascular smooth muscle, which increases intracellular calcium levels, leading to vasoconstriction [24]. In addition, it counteracts the effect of diabetes insipidus by acting on V2 receptors in the distal convoluted tubule of the kidney resulting in water reabsorption. Vasopressin has been associated with increased organ recovery and less overall graft refusal due to poor function [25, 26].

Diabetes insipidus

Endocrinopathy is common in patients with severe brain injury and after neurological death. The hypothalamic-pituitary axis is vulnerable to the effects of ischaemia and cerebral oedema, in particular the posterior pituitary structures, and paraventricular and hypothalamic supra-optic nuclei. Central diabetes insipidus occurs in 49–60% of patients with brain death [27], as a result of antidiuretic hormone depletion secondary to posterior pituitary failure. The prevalence of anterior pituitary failure, resulting in hypothyroidism and adrenal insufficiency, is currently unclear due to variability in the definitions used to describe these conditions [27, 28]. In addition, previous studies have demonstrated that many potential donors have variable residual anterior pituitary function left due to collateral blood supply from the internal carotid arteries [29, 30].

Central diabetes insipidus is characterised by polyuria (urine output $> 3\ l.day^{-1}$ or $3–5\ ml.kg^{-1}.h^{-1}$), hypernatraemia (serum sodium $> 145\ mmol.l^{-1}$), increased serum osmolality ($> 300\ mmol.kg^{-1}$) and low urine osmololality (urine specific gravity < 1.005 or osmolality $< 200\ mmol.kg^{-1}$) [2, 15, 28]. Loss of free water caused by diabetes insipidus can lead to profound hypovolaemia along with hypokalaemia, hypomagnesaemia, hypocalcaemia and hypophosphataemia. This can occur rapidly, and subsequent hypovolemia compounds the vasoplegic reduction in systemic perfusion pressure and cardiac output.

Treatment of central diabetes insipidus depends on the patient's haemodynamic status. In the absence of vasoplegia, desmopressin is recommended due to its greater affinity for V2 receptors located in the distal convoluted tubules and therefore exerts a predominantly antidiuretic response. An initial dose of 1–4 μg is recommended, followed by additional doses of 1–2 μg every 6 h titrated to effect [15]. Urine output, osmolality and serum sodium should be monitored closely to avoid deleterious consequences of fluid retention and hyponatraemia. Desmopressin also increases concentrations of factor VIII and von Willebrand factor [31]. This is often at higher doses of $0.3\ \mu g.kg^{-1}$. Theoretical concerns about potential thrombotic effects on graft survival are not supported by data from clinical trials [32–34]. Vasopressin

should be used if vasoplegia contributes to shock. Both treatments can be used concurrently in the presence of haemodynamic instability and severe hypernatraemia [15].

Corticosteroid treatment

Methylprednisolone attenuates the systemic inflammatory response following brainstem infarction [1, 35]. This response is mediated by production and upregulation of complement, cytokines, adhesions molecules, tumour necrosis factor, interleukin-6 and interleukin-8. Elevated donor interleukin-6 and interleukin-8 concentrations have been associated with early graft failure [36] and lower recipient survival [37]. Corticosteroid treatment may also improve haemodynamic stability and reduce vasopressor requirements [38].

Guidelines recommend administering high-dose methylprednisolone intravenously either as 1000 mg once daily, 15 $mg.kg^{-1}$ once daily or a 250 mg bolus followed by a 100 $mg.h^{-1}$ infusion [15]. It should be given after blood samples have been obtained for tissue typing as it may suppress human leukocyte antigen expression.

Despite being listed as a key objective for donor optimisation, there is a paucity of high-quality randomised data to support the routine administration of methylprednisolone. A systematic review of 11 randomised controlled trials found no evidence of an effect of corticosteroid treatment on vasopressor use, number of organs recovered, acute graft rejection or graft dysfunction [39]. The included studies included small patient numbers and were heterogenous in study design and adjuvant endocrine therapies. Only four randomised controlled trials were considered to be at low risk of bias and the overall quality of evidence was judged to be moderate or low for all outcomes. The review concluded that withholding or administering corticosteroids are reasonable courses of action.

The systemic sequelae of brain injury are not exclusive to patients with neurological death, with the subsequent release of catecholamines, cytokines and systemic inflammation. Moderate traumatic brain injury [40] or interrupted cerebral perfusion can also trigger inflammatory processes [41]. However, the period after confirmation of brain death is not only characterised by inflammation. Cytoprotective genes such as heme oxygenase-1 have been shown to be upregulated after induced brain death in murine models [42]. It is therefore possible that any beneficial effects of methylprednisolone are dependent on the timing of administration during the inflammatory response.

Respiratory management

Potential donors are at risk of neurogenic pulmonary oedema. High intracranial pressure and catecholamine storm result in raised hydrostatic pressures and pulmonary capillary damage [1, 43]. Additional pulmonary insults include ventilator-induced lung injury and increased expression of inflammatory mediators, pulmonary neutrophil infiltration and alveolar haemorrhage [44, 45]. The ventilatory goals of donor management are to maintain gas exchange to protect other organs and to preserve the lung itself.

Current recommendations of 'low-stretch' protocols, using lower tidal volumes, targeting plateau pressures < 30 cmH_2O and applying recruitment manoeuvres have been inferred from the improvements in outcomes seen in critically ill patients with the acute respiratory distress syndrome [46]. Historical guidelines recommended targeting tidal volumes of 10–15 $ml.kg^{-1}$ [47]. Such high volumes were later demonstrated to be an independent risk factor for developing acute lung injury in patients with severe brain injuries [48]. A subsequent multicentre, randomised controlled trial across 12 European ICUs showed that a lung-protective ventilation strategy roughly doubled the number of lungs transplanted when compared with a conventional strategy [49]. The trial was, however, stopped early due to termination of funding. The application of recruitment manoeuvres has been questioned in a recently published trial [50], which found that a titrated PEEP and lung recruitment manoeuvre strategy resulted in increased mortality in patients with acute respiratory distress syndrome. This suggests that knowledge from evidence in critically ill patients may not always be translatable to organ donor management, as important outcomes will be different.

Guidelines also advocate performing bronchoscopy in all potential lung donors to assess for infection and occult aspiration and for therapeutic airway clearance of mucous plugs and/or blood clots [15]. This is largely based on historical cohort studies which demonstrated improvements in oxygenation and use of donors who would not have otherwise been candidates for lung donation [51, 52]. It should be noted that routine bronchoscopy has not been shown to be of benefit in ARDS, indeed often causes significant de-recruitment predisposing to injurious ventilation and poor gas exchange [53]. Such historical guidance requires validation with robust randomised trial data. Other supportive therapies are summarised in Table 2 [54–58].

Table 2 Supportive measures for physiological optimisation of the potential donor after brain death.

	Suggested approach	Supporting evidence
Thyroid hormone replacement	A sick euthyroid syndrome is frequently seen in DBD donors, in the presence of an adequately functioning thyroid. Prolonged or severe hypothyroidism may impair cardiac performance. Current UK guidelines no longer include thyroid replacement	Observational data report an independent association between thyroid replacement therapy and higher numbers of procured organs, but these findings have not been replicated in RCTs [54]
Hyperglycaemia	Hyperglycaemia is common due to insulin resistance and can be further exacerbated by methylprednisolone administration. The ideal blood glucose concentration in donors is unknown. Therefore, in keeping with management recommendations from general ICU guidelines, blood glucose should be maintained between 4 and 10 $mmol.l^{-1}$ with an insulin infusion if necessary	Poor glycaemic control has been shown to be associated with impaired kidney and pancreas allograft function [55, 56]
Temperature	Active warming measures to target a temperature above 35 °C should be initiated to avoid adverse effects of hypothermia such as impaired myocardial contractility, acidosis and coagulopathy	Niemann et al. showed that mild therapeutic hypothermia (34–35 °C), when compared with normothermia (36.5 °C–37.5 °C), led to a significant reduction in the rate of delayed graft function in kidney transplant recipients [57]. There are no published results about impact on long term outcomes to date.
Anaemia and coagulation	Clinicians should apply recommendations from general ICU guidelines and apply a haemoglobin transfusion trigger of $< 70\ g.l^{-1}$ [58]. A higher trigger may be required if there is evidence of organ dysfunction, tissue hypoxia and/or profound haemodynamic compromise. Coagulopathy should be corrected in the presence of active bleeding and it seems reasonable to continue or start prophylactic low molecular weight heparin in the absence of bleeding	The optimal haemoglobin concentration in the donor population is not known as no RCTs have been conducted. Both disseminated intravascular coagulation, with a propensity towards bleeding, and a procoagulant state, have been observed in potential DBD donors. No specific treatment strategies to attenuate these processes have been investigated
General supportive care	Stop any unnecessary medications and actively identify and treat infection. Maintain gastrointestinal feeding where possible	Best practice guidelines

DBD, donation after brain death; RCT, randomised controlled trial.

Peri-operative considerations for organ donation surgery

Donor optimisation interventions initiated on ICU should be continued intra-operatively where possible. Maintaining stability throughout the peri-operative period allows for timely retrieval of organs in an undamaged condition [59]. A multiple organ procurement procedure will involve a single midline incision from the sternum to the pubis. There is potential for significant blood loss, hypothermia and haemodynamic instability. Spinal reflexes are common and can occur spontaneously or following surgical stimulus [60], therefore neuromuscular blockade is advised. Spinal reflexes can also lead to hypertension and increased plasma catecholamines. Hypertension can be treated with vasodilators, opiates or inhalational anaesthetic agents. As a result, there is considerable debate and variation in practice regarding the provision of anaesthesia, analgesia and neuromuscular blockade for donors after neurological death [61, 62]. A recent survey of French anaesthetists showed that sedatives, opioids and neuromuscular blocking agents were considered by 27%, 61% and 84% of respondents, respectively [63].

In addition to attenuating the sympathetic response, inhalational anaesthetic agents may also assist in remote preconditioning. One single-centre randomised controlled trial found that preconditioning with sevoflurane (end-tidal 2%) resulted in a lower incidence of early allograft dysfunction and lower peak transaminase levels in liver transplant recipients [64]. No long-term outcomes were analysed. Thoracic organs are usually retrieved first for reasons of tolerance to cold ischaemia. Intravenous heparin, at a dose of 300 $IU.kg^{-1}$, is given before aortic cross clamping, which will need to circulate for at least two minutes to reduce the risk of thrombus formation on retrieval. This practice is extrapolated from patients undergoing cardiac surgery [65].

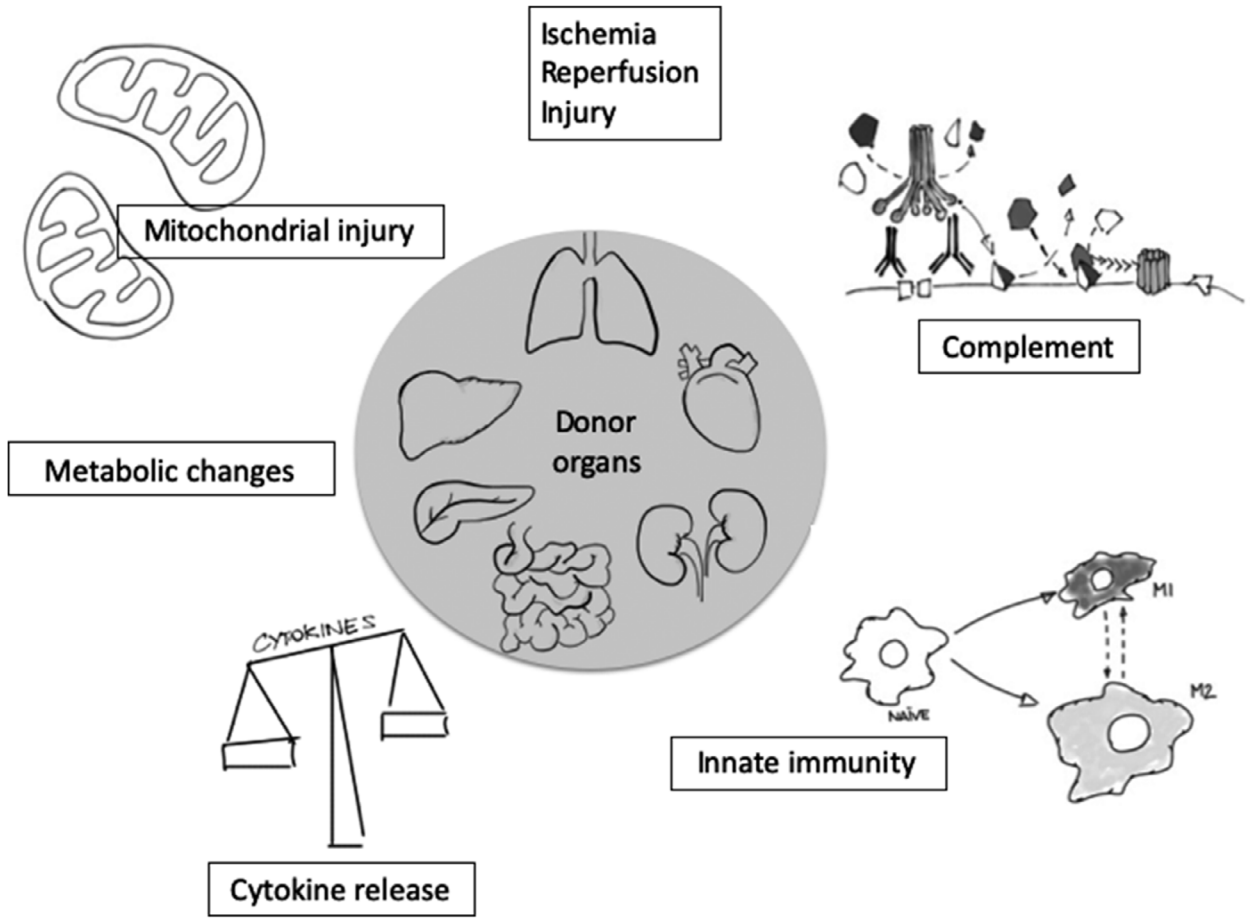


Figure 2 Overview of possible molecular and cellular targets for donor management intervention which could impact transplantation outcomes for all donated organs

The need for targeted evidence-based interventions

Adverse pathophysiological mechanisms activated by cerebral injury leading to brain death may immediately impact donation in two ways; either by affecting the decision to offer the organs for donation; or by increasing the likelihood of organs being declined due to donor instability or deranged biochemistry. Improvements in our understanding of the mechanisms underpinning organ injury offer the opportunity of novel therapeutic options (Fig. 2). The sequelae of activated pathways may also materialise in the medium or long-term period after transplantation and lead to a chronic decline in graft function characterised by chronic inflammation, deposits of collagen and fibrosis [66].

Recognition that HLA-mismatched live donor kidneys had superior outcomes compared with fully HLA-matched kidneys transplanted from deceased donors [67], led researchers to focus on the impact of donor condition and management on the quality of the potential grafts. In preclinical rodent models of brainstem compression a significant pro-inflammatory and pro-coagulatory response occurred following the massive catecholamine release during herniation of the brainstem, with a subsequent detrimental effect on the function and viability of kidney, liver, heart and lung [68–70]. These findings have been confirmed in human organ donors [71].

The pro-inflammatory donor environment leads to activation of complement; both animal and human work has demonstrated C3d and C5b-9 deposition in donor kidneys after brain death [72–74]. Complement inhibition in a rat model of kidney DBD showed reduced damage and inflammation as well as preserved renal function, albeit the inhibitor was administered before induction of brain death, which does not translate into applications with human donors. Human studies have demonstrated that complement activation, in both brain dead and cardiac dead donors, is associated with acute rejection of kidney transplants in recipients [75]. Targeting the complement system may therefore be a promising future donor organ optimisation strategy and phase-1 trials are currently

underway (see https://clinicaltrials.gov/ct2/show/NCT02435732) [76].

The influx of immune cells to the injured kidney can also contribute to early and late graft damage. The role of macrophage subtype switch from a pro-inflammatory M1 to an anti-inflammatory M2, which promotes tissue repair in recovery from sepsis-induced acute kidney injury, has been demonstrated in animal models [77]. A failure to switch can lead to progression towards chronic kidney disease characterised by fibrosis and glomerular and interstitial scarring [78, 79]. Immediate post-mortem human samples of kidneys in patients with sepsis-related acute kidney injury show increased glomerular M1 and M2 macrophages, suggesting inflammation and repair may be occurring simultaneously [80]. A systemic response to injury can also act by changing the local inflammatory response of tissue-resident macrophages and experimental data have shown that targeting macrophages may reduce complications following myocardial infarction, stroke and sepsis [81].

Outside the immune system, other important pathways that have been implicated in organ injury during donation and transplantation include ischaemia reperfusion injury, metabolic and mitochondrial injury. Akhtar et al. [82] demonstrated that brain death, induced in rats, leads to metabolic disturbances characterised by increased glycolytic protein expression and lactate production, alterations in mitochondrial function and increased reactive oxygen species generation. Mitochondrial damage has also been implicated in endothelial barrier dysfunction in animal models of lung transplantation after circulatory death [83]. Ischaemia reperfusion injury can lead to metabolic changes within the first 4 h after reperfusion as shown using proteomic analysis in a rat model [84].

Taken together, there is a multitude of promising targets for intervention worth exploring in clinical trials to investigate if organ damage can be prevented or regeneration encouraged in the donor. This can then inform future donor management bundles or even guide precision medicine approaches to improve organ quality and graft outcomes.

Research challenges

With better understanding of mechanisms of injury and repair and the opportunity to possibly prevent or reduce critical damage to organs being offered for transplantation, we need to understand how 'hostile' the condition of the donor truly is, whether organs need to be retrieved early or whether there is a window of opportunity for intervention. Retrospective studies have shown that a slightly longer duration of donor management did not necessarily result in

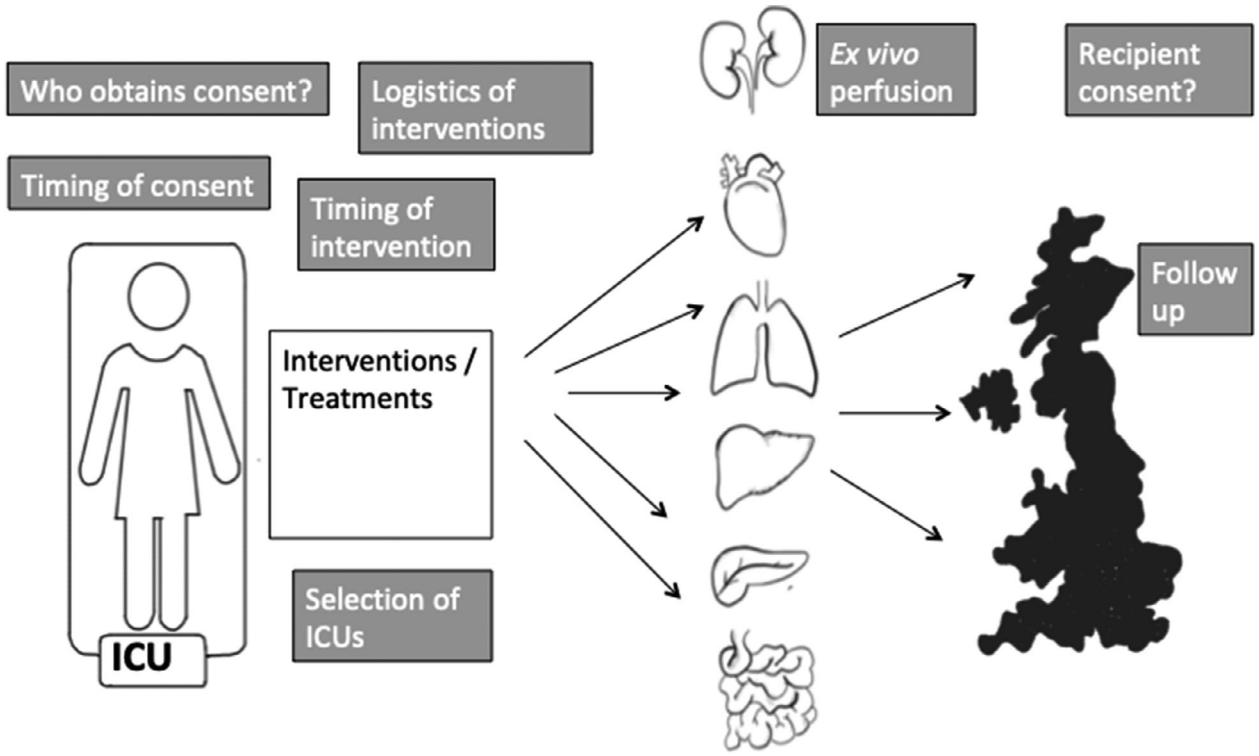


Figure 3 Summary of key research challenges in clinical trials evaluating deceased donor management interventions.

inferior function or graft survival for liver and pancreas transplant, and for kidney and heart transplantation, registry data suggest that a stable slightly prolonged period of donor management might be beneficial [85–87]. However, overall the evidence to suggest deviation from current practice remains weak and studies ought to address the ethical and logistical implications relating to timing and duration of any donor intervention.

Testing new therapies in clinical trials involving the deceased donor also creates challenges that do not apply in other settings (Fig. 3). Some of those are not dissimilar to difficulties regarding clinical trials in critical care and include: a heterogenous patient population; time-critical decision-making; limited ability to obtain consent when treating incapacitated patients; and difficulties in collecting long-term outcomes [88–90]. Other challenges, however, are rather unique to the field of donor management research and organ transplantation.

The application of the principle of informed consent is complex in the DBD organ donor. Ideally, prior consent to interventional research after death to facilitate donation and transplantation would have been sought, much as we seek consent for the donation itself via the organ donor register. There is no provision for this in the UK, or any realistic likelihood of achieving it, and so consent for research is sought from the donor's family after diagnosis of death, as outlined in the Human Tissue Act (of note this will still be required after the recent Organ Donation (Deemed Consent) Bill) [91]. After diagnosis of death based on neurological criteria, the donor is beyond physical harms that might ensue as a result of research interventions. However, many families and cultures might differ with this narrow medical interpretation of harms, and the donor's altruistic wish to donate as many organs as possible must also be considered implying that no research intervention should compromise the safe donation of a particular organ. There is evidence that the families of critically ill patients struggle to make decisions related to incapacitated patients, even when there is potential to discuss their decision with them at a later date [92]. On the other hand, the experience with the UK national bioresource for quality in organ donation (QUOD) (see https://quod.org.uk) that collects research samples from deceased donors and donor organs demonstrates that, if consent for organ donation is given, authorisation for research sample collection is also given in approximately 90% of the cases [93].

A patient's voluntary informed consent to research is deemed 'absolutely essential' according to the Nuremberg Code [94]; however, research ethics committees have permitted deferred consent successfully in clinical trials evaluating emergency treatments where seeking consent is impractical [95]. Approaching relatives for deferred consent could be traumatic. It might be counterproductive at a societal level with more prospective donors opting out of the donor register due to concern about research without a priori consent, even though research is specifically excluded from the recent Deemed Consent legislation [96]. This does not appear to have been the case with 'deemed consent' legislation as introduced in Wales. Donor families may appreciate the opportunity to support transplant-related research as it aligns with the donor's altruistic wish to improve the viability of donated organs and increase organ utilisation. Qualitative research of deferred consent given by parents after randomisation of their children to an emergency treatment showed that timing of the consent discussion was paramount; this was particularly emphasised by the bereaved parents [97]. Healthcare providers also expressed apprehension about approaching bereaved next of kin for deferred consent further emphasising the ethical concerns about using this approach. Determining the most appropriate mechanisms for seeking consent from donor families at a very stressful and emotional time is a key research priority [91], especially as the opportunities described below become realistic prospects. As in matters of consent for a clinical procedure and for research in general, in research for organ donation the trust between the family (on behalf of the patient) and the healthcare providers remains paramount.

Consideration should also be given when donor (organ)-related research may affect the recipient of a particular organ. When the majority of interventions occurs in the donor, most of the potential recipients will be unknown. The mean number of organs donated per donor in the UK is 3.7 [98]; therefore, seeking research consent from potential organ recipients within the pathway would either not be possible or add significant complexity as entire national waiting lists would require consent for a research project in which only a few recipients are likely to be involved. However, as the benefits (and potential harms) of interventions may affect the organ to be received by the recipient and therefore influence his or her decision to accept an organ, it is an area worthy of further discussion. Assuming that it would be impractical to look for recipient consent before intervention in the donor and that donor family research consent rates remain high [99], a recipient refusal is very likely to adversely impact their chances of receiving an organ. How independent and free is their consent in such a scenario?

Donor management research also poses unique logistical and practical challenges. There is huge variation in

numbers of donors per ICU per year. Feasibility assessment would minimise cost and study duration by inclusion of only high-volume units, but also exclude large numbers of potential donors and potentially study applicability. Further considerations include identification of research team members to seek consent (and whether they are locally or regionally based) as well as transportation and storage of all required equipment or treatments to participating units. Local storage allows time-critical application of treatments but requires multiple units to have expensive equipment. As organs are to be transplanted across the nation, follow-up beyond the scope of routinely recorded outcome data within NHS Blood and Transplant might prove difficult.

Opportunities

Despite the outlined challenges with research in intensive care, and donor management in particular, we believe that the UK system of donation and transplantation offers some important opportunities. The UK has a national organisation, NHS Blood and Transplant, which is responsible for education, delivery and governance of donation and transplantation. This custodian role includes management of several databases which routinely collect vast quantities of data, including the Potential Donor Audit (including every death in ICU and Emergency Departments), Donor Path (pathophysiology in potential organ donors) and the UK National Transplant Database (NTxD; every UK transplant). In addition, the Quality in Organ Donation (QUOD) project has been successfully incorporated with the organ donation and transplantation process, engaging many units with research and collection of samples [93]. Research consent rates for the QUOD biobank from donor families is very high at > 85%, suggesting patient and public willingness to participate in research and quality improvement. This is probably in part due to the dedicated information given by the experienced and compassionate personalised care offered by a national network of specialist nurses for organ donation.

Linking biological data with epidemiological and patient-level information from NHS Blood and Transplant in a coded anonymised fashion, organ-specific registries and intensive care datasets may allow development of prognostic models for optimal outcomes in organ transplantation [100]. Indeed, granular detailed description of donor physiology, immunology and response to intervention may be key to facilitate improvements in organ assessment, acceptance and utilisation.

Finally, the UK has truly embraced collaborative research in the last decade: both trainee-led collaboratives and more senior researchers via National Institute for Health Research (NIHR) Clinical Research Networks have delivered large-scale national projects [101, 102]. This has also allowed medical professionals to engage with clinical research as part of their professional training and has improved access to research involvement [103].

The development of a new UK Organ Donation and Transplant Research Network (UKODTRN) is a crucial component of this, building on the existing infrastructure, national organ donation architecture and experience from collaborative research. Working with resources such as a QUOD and learning from their expertise will be important when supporting mechanistic research of organ donor management. Some of the suggestions to improve recruitment in ICU [104] can be directly translated, whilst other areas require further feasibility work and qualitative research involving donor families, clinical staff and recipients. Looking outside of Europe, we are likely to learn important lessons from a national observational study in Canada [105] that has recently completed recruitment and was designed to describe current organ donation practices, evaluate the effectiveness of interventions and assessed the feasibility of future randomised trials.

Conclusion

Currently available donor management interventions have not demonstrated improvements in immediate post-transplant function and long-term graft or recipient survival, but they have been inadequately tested to date. The prevention of injury and promotion of repair before organ retrieval by targeting specific pathological pathways, such as inhibiting complement activation, offer novel pathways for donor management research beyond physiological stabilisation. There are a number of ethical, logistical and legal hurdles to be considered to facilitate and incorporate clinical research into the management of deceased donors. The UK organ donation system, coupled with a strong anchoring of evidence-based medical practice into postgraduate training, offers a solid foundation for establishing a national organ donation research network. This would enable us to answer critical questions which will benefit patients on the waiting list and after transplantation while respecting the donor and their family's wishes.

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