British Transplantation Society guidelines on abdominal organ transplantation from deceased donors after circulatory death

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Review article

British Transplantation Society guidelines on abdominal organ transplantation from deceased donors after circulatory death

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ABSTRACT

The British Transplantation Society (BTS) 'Guideline on transplantation from deceased donors after circulatory death' has recently been updated and this manuscript summarises the relevant recommendations in abdominal organ transplantation from Donation after Circulatory Death (DCD) donors, encompassing the chapters on liver, kidney, pancreas and islet cell transplantation.

1. Introduction

The British Transplantation Society (BTS) 'Guideline on transplantation from deceased donors after circulatory death' has recently been updated [1] and this manuscript summarises the relevant recommendations in abdominal organ transplantation from Donation after Circulatory Death (DCD) donors, encompassing the chapters on liver, kidney, pancreas and islet cell transplantation.

2. Methods

The BTS 'Guideline on transplantation from deceased donors after circulatory death' was written in line with the BTS guideline development policy, and the recommendations of NICE Evidence [2]. Contributors of the guideline conducted their own literature search using PubMed® to identify relevant evidence. Virtual progress meetings between the guideline development group and contributors were held. A face-to-face meeting was then held for review and discussion of the final grading of the recommendations. Comments on the preliminary draft were invited from patient representatives. The Guidelines were further edited and opened for public consultation through the website of the BTS. In these Guidelines the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system has been used to rate the strength of evidence and the strength of recommendations [3].

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3. Adult recipient liver transplantation

3.1. DCD liver donor selection

We recommend that:

- All centres should be prepared to use livers from DCD donors for transplantation. (1B)

We suggest that:

- DCD donors may be used without an age limit if other surrogates of donor organ quality are favourable. (2B)
- High donor BMI is a risk factor for graft loss both in DCD and DBD donation, therefore a higher BMI alone should not be a contraindication for accepting a DCD graft if other factors are favourable. (2B)

Donor age has played an important role in risk stratification, and in the early era, donors >50–60 years old were considered high risk [4,5]. Recent experience and published literature suggest that good outcomes with older DCD can be achieved [6]. Therefore, the influence of donor age (namely >60 years) on the results of liver transplantation using a DCD graft is debatable. We would suggest the use of DCD donors without age limit if the rest of the donor demographics and other variables (*e.g.*, ischaemic times) are favourable.

Donors with high BMI are considered to be at risk of graft loss in DCD transplantation as well as DBD. A higher BMI is likely to be a surrogate for steatosis in liver grafts. Previous experience has shown a negative impact of donor BMI >25 kg/m^2 at any donor age on graft and patient survival [4]. However, more recent studies have demonstrated good outcomes with DCD grafts from donors with BMI >35 kg/m^2 [7]. We would suggest that donor BMI alone should not be a decision-making factor in DCD liver transplantation.

3.2. DCD donor warm ischaemia times

We recommend that:

- If the donor functional warm ischaemia time (FWIT) exceeds 30 min and organs are not being recovered using *in situ* normothermic regional perfusion (NRP) or *ex situ* hypothermic machine perfusion (HMP), there is an increased risk for graft loss, however further donor and recipient characteristics should be taken into account before considering rejecting the graft in borderline cases. (1B)

We suggest that:

- Serial blood gases during the withdrawal phase should be used as an additional tool to determine the onset of anaerobic respiration by providing lactate measurements. (2D)

The withdrawal time is defined as the time from donor withdrawal of treatment to initiation of cold perfusion or the start of NRP. The FWIT starts when the systolic blood pressure has a sustained (*i.e.*, at least 2 min) fall below 50 mmHg and extends up to the onset of cold *in situ* perfusion or NRP [8].

It was seen in previous studies that the duration of SBP <50 mmHg is directly correlated with increased rates of ischaemic cholangiopathy (IC), graft loss or death and there is no new solid evidence to suggest that these thresholds should be changed when traditional rapid recovery is employed [9].

3.3. DCD donor hepatectomy time, and time between donor hepatectomy and into the ice box

We suggest that:

- The emphasis should be on minimising donor hepatectomy time; in ideal scenarios, hepatectomy time should not be longer than 30 min. A longer hepatectomy time is associated with graft failure in non-NRP DCD donors. (2C)
- Time between knife-to-skin and liver placement into the ice box should ideally be less than one hour; this is a target that all retrieval teams should be encouraged to achieve. (2B)

In a study performed by Farid et al., the median donor hepatectomy time (DHT – time between start of cold perfusion to liver on the back-table) was 35 min and in the multivariate analysis, the factors associated with graft survival were hepatectomy time longer than 60 min, donor older than 45 years, CIT longer than 8 h and recipient with previous abdominal surgery [10].

Goussous et al., have described in a comparative retrospective review (historic group before 2014 and modern group after 2014) that when DHT was dichotomized at <22 min *versus* >22 min, a longer DHT was associated with development of IC [11].

Evidence is still less clear at which point exactly the DHT starts to have a detrimental effect. Gilbo et al., suggested that there is a linear relationship between DHT and IC and there is a 19% increment in the rate of IC for every 10 min increase in DHT (this effect is similar to a one-hour increase in CIT) [12]. Other studies have reported that DHT is a significant independent risk factor for IC after DCD liver transplantation [13].

A key period is also the time from aortic/portal flush *in situ* until the liver is placed into the transport ice box and in the previous study that further time was a median of 33 min [12]. Although the fluid in the bowl is cold this is not enough to guarantee that rewarming of the graft doesn't occur causing a deleterious effect on bile duct viability. Therefore, we would suggest aiming for no more than one hour from knife-to-skin to liver placement into the ice box time as an achievable target that all retreival teams should be encouraged to achieve. This requires good coordination, communication and teamwork between surgeons and other members of the scrub team.

3.4. Use of ex situ machine perfusion

- *Ex situ* preservation time can be extended beyond 8 h when *ex situ* machine perfusion is used, but the impact on IC is unknown. (1B)

Ex situ machine perfusion is a preservation method occurring outside the donor's body, developed to protect organs from the detrimental effects of ischaemia-reperfusion injury (IRI), enable assessment of function, and facilitate the repair/regeneration of DCD grafts in order to expand the donor pool and improve graft function after liver transplantation. *Ex situ* machine perfusion may be at normal body temperature (normothermic) using a blood-based perfusate, this is termed normothermic machine perfusion (NMP). *Ex situ* machine perfusion may also be hypothermic, termed HMP. The current evidence favours oxygenating the perfusate, a technique called hypothermic oxygenated machine perfusion (HOPE), running at a temperature of 4 to 10 °C. NMP offers the advantage to assess graft viability under more physiologic conditions [14].

3.5. DCD donor liver retrieval

We suggest that:

- Dual aortic and portal perfusion during DCD liver retrieval and flushing of the bile duct should be standard. (2C)

In order to minimise the detrimental effects of warm ischaemia, the abdominal organs are required to be immediately flushed with an ice-cold preservation solution as soon as possible after death has been declared. As a result of the donor warm ischaemia, ATP levels are

progressively depleted.

Some authors have recommended dual perfusion during DCD liver retrieval, and this is recommended in National Health Service Blood and Transplant (NHSBT) guidance. Although the evidence supporting this practice is relatively limited [15,16], we suggest that dual perfusion during DCD liver retrieval should be the standard.

3.6. Immunosuppression

There is currently no evidence indicating that there should be a difference in the immunosuppression protocol for DCD when compared to DBD liver transplantation.

3.7. Outcomes of DCD donor liver transplantation

We recommend that:

- The outcome of transplanting DCD livers recovered without NRP is improved with short CIT, and that CIT should be kept under 8 h. (1B)
- *Ex situ* preservation time can be extended beyond 8 h when NRP has been used. (1B)
- The use of *in situ* NRP and *ex situ* HMP can reduce the incidence of symptomatic IC when compared to static cold storage. (1 A)
- The use of NRP is an effective way to increase the number of viable livers recovered. (1B)
- Future studies evaluating the possible mechanisms protecting against IC in DCD donors are needed. (1B)

We suggest that:

- The total preservation time could be extended beyond 8 h if any of the machine organ preservation techniques are utilised, but there is no recommendation of a safe upper limit of preservation based on current evidence and this should be at the discretion of the implanting surgeon. (2D)
- Potential recipients of DCD liver grafts which have not been subject to *in situ* or *ex situ* perfusion should be informed of the potential risk of both early and late graft loss. (2C)

We have observed an improvement in graft survival in DCD recipients over the last decade, mainly in the first year of transplantation [17]. One of the major improvements from a procurement and organ preservation point of view has been the use of NRP combined and/or *ex situ* machine perfusion. The use of NRP has improved not only organ utilisation but also survival outcomes. From 1470 DCD first liver transplants, 94 (6%) were recovered in NRP. In the NRP group, the event death or graft loss within 12 months was 7% *versus* 13% in the non-NRP group [18].

4. Paediatric recipient DCD donor liver transplantation

We recommend that:

- Excellent short- and medium-term outcomes can be achieved in paediatric DCD liver transplantation with highly selected and careful donor and recipient selection. (1B)
- Use of paediatric or young adult DCD grafts is an effective approach to expand the donor pool and remains an underutilised resource for children in need of liver transplantation. (1B)
- An international registry of paediatric DCD liver transplant recipients is needed to determine whether there is a significant difference in outcomes from DBD transplantation. (1B)
- A national differential analysis of outcomes in paediatric DCD liver transplantation is required, depending on whether a paediatric or an adult DCD is used. (1B)

We suggest that:

- DCD livers can be used in children as whole, reduced or split grafts, if they are of excellent quality, the FWIT is <30 min and the CIT <8 h. (2B)
- The recommended criteria considered for appropriate donor selection in children in the UK are: Donor age < 40–45 years-old, ITU stay <5 days, normal liver function tests, FWIT <30 min, normal liver appearance and perfusion after recovery. (2B)
- Paediatric DCD livers recovered without NRP are less likely to present with IC as they may be more resilient to IRI and have higher regenerative capacity. (2B)
- Machine perfusion in paediatric liver transplantation can play a role in halting the effects of the CIT, improving the liver quality in whole grafts for older children or young adults, and facilitating splitting and utilisation of both lobes. (2C)

The burden of the paediatric liver transplant waitlist does not exceed 50 patients and waitlist mortality is <5% *per annum*. For reasons of early inferior outcomes, the use of DCD liver grafts in the paediatric population should be done only in highly selective situations. Despite the good outcomes reported by different centres, the decision to use DCD livers in critically ill children should be taken carefully, analysing the risk-benefit case-by-case, and when a good quality DBD liver or a suitable living donor is not available in a timely manner. The main controversies when utilising DCD livers in children are the difficulty to find a size-matched graft in case of requiring an emergency re-transplantation for PNF or hepatic artery thrombosis (HAT), and the unknown long-term outcomes of these grafts in patients likely to have a longer life expectancy when compared to the adult population. Despite the limited experience around the world in paediatric DCD liver transplantation, single-centre series reported by large volume transplant units have published patient and graft survival rates of 100% at three-years follow-up, with no increased incidence of PNF, vascular complications or biliary complications [19,20]. Different authors have shown the feasibility of splitting a DBD liver during HOPE, with the possibility of removing the left lateral segment from the circuit first, allowing the right lobe to stay perfused until it is utilised or put in the ice box to be transported to another centre. The feasibility of splitting livers during *ex situ* NRP has also been demonstrated [21].

5. Kidney transplantation

5.1. DCD kidney donor selection

We recommend that:

- Contraindications to kidney donation do not differ according to deceased donor type. (1B)

We suggest that:

- The use of kidneys from DCD donors with AKI should be considered in the context of individual recipient factors. (2B)

With the expansion of the donor pool, the utilisation of kidneys from sub-optimal donors is becoming increasingly common. The use of kidneys that are identified as ‘higher risk’ of graft loss should be weighed against the risks of remaining on the deceased donor kidney transplant waiting list or the realistic probability of receiving a better offer within an acceptable time frame.

Donor and retrieval factors that impact graft outcomes include donor age and CIT [22,23]. Additional factors such as donor hypertension and cardiovascular disease have also been shown to have an impact on DCD kidney survival, but to a lesser degree [23].

The effect of donor AKI on transplant outcomes has been examined in

large registry studies. A large UK-based study [24] showed that rates of primary non-function (PNF) and delayed graft function (DGF) were not independently associated with DCD *versus* DBD donation, and reported good outcomes from kidneys with AKI stages 1–2. A more recent US study has shown a higher rate of graft failure in DCD kidneys with AKI stages 1–2 compared to DBD kidneys, but better patient outcomes than remaining on the waiting list [25].

5.2. DCD donor kidney warm ischaemia time

We suggest that:

- The use of kidneys from donors with a withdrawal time >3 h or absent blood pressure for >30 min should be restricted to protocols that attempt to resuscitate organ viability. (2C)

A recent large cohort study of patients from the UK transplant registry examined 10,000 deceased donor warm ischaemic times, including 3000 DCD donors [26]. This study showed that although DCD donor kidneys were associated with a higher risk of DGF, this was highest when FWIT exceeded 30 min, with DBD donors used as a comparator group (OR 5.8 95% CI 2–8-12.1). However, there was no demonstratable difference in PNF or medium-term graft survival.

The use of kidneys from DCD donors with >30 min of absent blood pressure may be considered in programmes which are undertaking measures to 'recondition' organs *via ex situ* oxygenated normothermic perfusion, with the possibility of a more predictive assessment of organ quality.

5.3. DCD donor kidney retrieval

We suggest that:

- NRP may reduce the incidence of DGF and improve kidney function in DCD kidneys. (2B)

Retrieval from controlled DCD donors employs a 'super-rapid' retrieval technique to minimise warm ischaemic damage, however, there is significant inter-clinician variability in how this is achieved. Inadvertent injury to the kidney is higher in DCD donors relative to DBD donors [27]. The use of NRP in DCD donor transplantation is associated with a longer asystolic time but the impact of this is nullified by avoiding a period of CIT immediately afterwards.

In a UK registry study, 5954 first kidney-only transplants were undertaken from DCD donors and NRP was used prior to 210 kidney transplants (4%). In risk-adjusted analyses, NRP kidneys had a 35% lower chance of developing DGF than non-NRP kidneys (odds ratio, 0.65; 95% CI, 0.47–0.90), and the expected 12-month estimated glomerular filtration rate was 6.3 mL/min/1.73m^2 better if abdominal NRP was used ($p < 0.0001$) [18].

5.4. Organ preservation

No definitive data currently suggest any advantage for specific preservation solutions in the context of DCD kidney transplantation [28,29] despite the wide variation in cost.

5.5. Organ quality assessment

We recommend that:

- The incidence of DGF is 40–50% in recipients of kidneys from DCD donors and this should be discussed with the patient prior to transplantation. (1 A)

After transplantation, kidneys may work immediately, recover after a period of impaired or absent function, or never function at all. Early function is dependent upon the underlying health of the donor as well as the ischaemic time, any damage sustained during the process of death and organ retrieval, as well as operative, immunological, and recipient factors. Because of the availability of dialysis to support initial graft dysfunction, the emphasis in kidney transplantation must be on minimising, and as far as possible eradicating, PNF.

5.6. Viability assessment from perfusion parameters and biomarkers

We suggest that:

- None of the HMP perfusate effluent biochemical analysis/perfusion pressure dynamic characteristics, or kidney transplant biopsy scoring systems - alone or in combination - have sufficient predictive value to mandate organ discard. (2 A)

There has been significant interest in whether information gained during machine perfusion may enable organ viability assessment.

In cold machine perfusion, a European cohort study examined the performance of 336 deceased donor kidneys to determine whether kidney vascular resistance could predict DGF [30]. This study showed that renal resistance was an independent predictor of DGF on multivariable analysis. However, analysis of received operator characteristic curves showed a low predictive accuracy for DGF (area under the curve 0.58). Existing studies examining early biomarkers of DGF and PNF are limited in quality and have not been found to be highly predictive of post-transplant outcomes [31].

In *ex situ* warm machine perfusion, kidneys are thought to be put in a functional state, allowing urine output, and macroscopic appearance to be examined, in addition to kidney blood flow. In a study of 74 human kidneys, critical thresholds associated with superior graft function were determined [32].

5.7. Viability assessment from biopsy parameters

We suggest that:

- None of the kidney transplant biopsy scoring systems - alone or in combination - have sufficient predictive value to mandate organ discard. (2 A)

Work on the assessment of organ quality from histological parameters is mainly derived from the examination of extended criteria donors (ECD), rather than specifically in relation to DCD, organs. There is conflicting evidence on whether the routine use of pre-implantation kidney biopsies improves graft outcomes. The effect of provision of a national donor kidney histology service on the organ utilisation of kidneys offered from deceased donors aged over 60 years is currently being investigated (Pre-Implantation Trial of Histopathology In renal Allografts – PITHIA; ISRCTN11708741) [33].

Composite scores combining donor histology with other donor and recipient characteristics may provide the best predictive value. An international cohort study examining eight functional, histological and immunological prognostic factors have been combined to produce a graft survival prediction score with good predictive accuracy (C-statistic 0.81) [34].

There are currently no histological markers that predict PNF as a result of excess warm ischaemia or irreversible IRI.

5.8. Clinical donor risk scores

A range of increasingly complex scoring systems have been developed in an attempt to predict outcomes in relation to pre-existing donor factors. These are not specific for use in the context of DCD kidney donation [35]. No scoring system, either alone or in combination with

pump parameters or histological scoring, has yet been shown to accurately define which organs should be discarded due to an excessive risk of PNF or seriously impaired long-term graft function [22].

5.9. Ex situ machine perfusion

We suggest that:

- HMP may reduce the incidence of DGF in recipients of DCD donor kidneys when performed from the point of retrieval. (2B)

A recent Cochrane review and meta-analysis has shown that cold machine perfusion is protective against DGF in DCD donor kidneys (RR 0.75, 95% CI 0.64–0.87) [36]. This work suggests that seven perfusions are needed to achieve immediate graft function in one DCD donor kidney, compared to static cold storage alone. There is no demonstrable advantage of oxygenated HMP compared to non-oxygenated in ECD [37].

A multicentre open-label randomised control trial examined the use of *ex situ* warm machine perfusion prior to DCD donor kidney transplantation, compared to static cold storage alone [38]. Kidneys randomised to warm machine perfusion were perfused for one hour with an oxygenated red blood cell-based solution at 36.0 °C. There was no demonstrable reduction in DGF between kidneys undergoing warm machine perfusion compared to static cold storage alone.

5.10. Recipient selection

We recommend that:

- Potential recipients should be informed that long-term outcomes for standard criteria donors are equivalent for DCD and DBD kidney transplants. (1 A)

UK registry data show that the incidence of DGF in DCD recipients ranges from 39 to 50% compared with 25% in DBD recipients [22,39]. In the UK, current data suggest that recipients of DCD kidneys have similar longer-term outcomes to recipients of DBD kidneys [22].

5.11. Immunosuppression

We recommend that:

- There is no evidence to support the use of alternative immunosuppression strategies in DCD donor kidney transplants beyond the standard of care. (1B)

5.11.1. Use and choice of induction therapy

Induction therapy with either IL2-receptor blockade or lymphocyte depletion has previously been shown to reduce DGF in retrospective studies of DCD kidney transplants [40,41], and has been recommended in earlier guidelines. No single agent has been shown to be superior in the setting of DCD kidneys.

More recently induction therapy with basiliximab is recommended in NICE guidance [42] and is now considered to be standard of care for the majority of transplants in UK transplant centres, regardless of donor type.

5.11.2. Choice of calcineurin inhibitor

The studies comparing immunosuppression regimens in DCD renal transplantation are largely retrospective, and from an era when DCD outcomes were inferior to now. The theoretical advantages of minimising exposure to calcineurin inhibitors (CNIs) in the early post-operative period have not been convincingly demonstrated in practice to date.

Early sirolimus use is associated with increased adverse events including prolonging DGF and acute rejection [43] and is not recommended.

5.12. Outcomes of DCD donor kidney transplantation

We recommend that:

- Long-term outcomes of DCD recipients are similar to those of DBD recipients and the allocation system for DCD and DBD donor organs should be similar. Nevertheless, it is recognised that DCD donor kidneys are more susceptible to cold ischaemia than DBD kidneys, and should be implanted <12 h, where possible. (1B)

Overall graft outcome after transplantation is primarily determined by the quality of the donor rather than the mode of donation [22,44]. ECD kidneys are associated with inferior graft survival compared to SCD kidneys, irrespective of DBD / DCD status [44]. As well as graft survival, longer-term graft function is also similar. GFR is initially poorer because of the high incidence of DGF in DCD, but is equivalent after 3 months. Despite the increased incidence of DGF in recipients of DCD donor kidneys, there does not appear to be a graft or patient survival disadvantage in the majority of DCD donor kidney recipients relative to DBD donor kidney recipients [22,45]. Considering DGF duration in DCD donor kidney transplantation reveals that DGF lasting <14 days is not associated with inferior graft or patient survival [39]. In DCD donor kidney transplantation, recipients with DGF lasting >14 days are at a significantly higher risk of graft and patient loss. NHSBT data show that increasing donor and recipient age and a cold ischaemic time of >12 h are associated with a worse outcome [22].

5.13. Paediatric recipient DCD donor kidney transplantation

We suggest that:

- In paediatric recipients, the rate of DGF and PNF is higher in DCD donor kidneys compared to DBD donor kidneys. However, three-year graft survival is comparable. (2B)

The use of DCD donor kidneys for paediatric recipients is relatively uncommon, making up <2% of paediatric kidney transplants, primarily due to concerns about PNF and DGF. In paediatric recipients, the rate of PNF is 5% and the rate of DGF is 25% [46]. However, following cautious DCD donor selection, there are comparable three-year survival rates to matched DBD donor kidney recipients.

6. Pancreas transplantation

6.1. DCD pancreas donor selection

We recommend that:

- Pancreas transplantation from DCD donors offers similar outcomes to DBD donors, in terms of graft and patient survival, and therefore DCD donors should be considered an acceptable source of pancreatic grafts. (1B)
- Although DCD organs can be used for solitary pancreas transplantation, numbers are limited, and therefore most evidence supports their use for the simultaneous pancreas and kidney (SPK) transplantation. (1C)

Over the last decade in the UK, pancreatic transplantation from DCD donors has been performed at relatively steady numbers of around 50 per year, comprising roughly a quarter of the total number of pancreatic transplants [47]. Worldwide, the number of DCD pancreas transplants remains low compared to DBDs.

Most of the published outcome data come from the USA and the UK. These suggest that outcomes from DCD SPK transplantation are comparable to those of DBD SPK transplantation. The results of pancreas transplantation alone (PTA) are worse than those of SPK transplantation. However, the outcomes after DCD PTA are not significantly worse than that of DBD PTA [48].

The selection of DCD donors for pancreas transplantation has been more restrictive than that for DBD donors. Admittedly, expected pancreas CIT remains a major factor involved in decision-making at the time of a DCD pancreas offer and is largely influenced by the availability of virtual cross-match, travel time to recipient centres and local arrangements of surgical teams.

The number of PTA or Pancreas After Kidney (PAK) transplants from DCD donors is much smaller, and does not allow a rigorous analysis of factors affecting donor selection, but the following broad comments reflect current experience and practice in the UK with SPK transplants, which represent 90% of pancreas transplant activity. UK data suggest a poorer outcome for DCD PTA [48].

Suggested donor criteria for pancreas transplantation are shown in Table 1, based on rapid recovery. However, this is an evolving field, and some of these variables may alter if the pancreas is recovered using NRP. It is important to note that transplanting centres in the UK will have built up a volume of expertise with ECD DCD criteria, and these criteria should not restrict innovation.

6.1.1. Age

UK transplant registry data suggest that increasing donor age remains a significant factor contributing to transplant outcomes for DCD pancreata in the UK. Current criteria are to consider all potential donors up to the age of 60 years, although an increased risk of pancreas graft loss should be taken into account when selecting donors older than 50 years (HR 2.28, 95%CI 1.60–3.26; $p < 0.01$) [49].

6.1.2. BMI

A low donor BMI (<28 kg/m^2) is preferred, but potential donors with higher BMI should still be referred and organs should be considered for acceptance when the donor BMI is ≤30 kg/m^2. Pancreata from donors with a BMI >30 kg/m^2 should be referred for consideration of islet transplantation, as per the UK national pancreas offering scheme.

6.1.3. Time post-withdrawal

A prolonged FWIT is a reasonable indication to abandon pancreas retrieval. Otherwise, a donor in whom the blood pressure is stable may still yield a transplantable pancreas sometime after treatment withdrawal. In general, the retrieval team should be prepared to retrieve the pancreas for up to three hours following the withdrawal of support. The decision to stand down sooner should be made on the basis of the blood pressure profile and after consideration of other potentially adverse donor criteria. Pancreata from donors with a withdrawal period of over 60 min have been used for transplantation successfully [47,48].

6.1.4. Inotropes

Although high doses of inotropes are generally agreed to be detrimental, there is no good evidence on which to base national criteria. Inotrope levels should not, therefore, be used to exclude the referral of DCD donors for pancreas retrieval.

6.1.5. Amylase and glucose levels

There is no good evidence that the level of either amylase or glucose has prognostic significance, and these should not be used to exclude either the referral or the transplantation of DCD donor pancreata.

6.1.6. Steatosis and fibrosis

These factors are largely subjective and difficult to quantify, and the precise significance of differing degrees of steatosis or fibrosis are uncertain. For these reasons, retrieval should proceed unless the changes are obvious.

Table 1
Donor criteria for pancreas transplantation.

Donor variables	Ideal DCD	Marginal (ECD) DCD
Age (years)	< 45	45–60
BMI (kg/m^2)	< 28	28–30
FWIT (min)	≤ 30	> 30
Expected CIT (hr)	≤ 10	> 10
Steatosis	None	Mild-moderate
Recommendation	*All potential pancreas donors fulfilling these criteria should be used*	*These grafts should be considered after careful assessment*

6.2. DCD pancreas preservation

We recommend that:

- Outcomes of DCD pancreas transplants are better with lower CIT and, ideally, this should be kept to within 10 h. (1B)

We suggest that:

- Pancreas transplants from DCD donors are at increased risk of reperfusion pancreatitis and thrombosis and this may be exacerbated by prolonged CIT >12 h and increasing donor age > 55 years. Ideal donors should be <45 years old and have a BMI <28 kg/m^2. (2C)

There is good evidence that cold ischaemia is detrimental to the outcome of pancreas transplantation in proportion to its duration. CIT remains one of the main predictors of pancreas graft failure. UK data suggest that, when DBD and DCD grafts are combined, a CIT of >12 h is associated with a significantly increased risk of graft loss (HR 1.80, 95% CI 1.04–3.07) [49]. A shorter CIT (ideally up to 10 h) may be more appropriate for DCD SPKs, though the previous analysis was unable to identify a CIT beyond which DCD donor pancreas graft survival deteriorates.

6.3. DCD pancreas quality assessment

There is no 'standard' quality assessment. Assessment is largely based on visual inspection and clinical experience.

6.4. Recipient selection

We suggest that:

- There is limited evidence regarding the effect of recipient risk factors in terms of outcome after DCD pancreas transplantation, however, we would recommend considering the same risk factors as those that may contribute to an adverse outcome after DBD pancreas transplants (*e.g.*, higher recipient BMI, cardiovascular morbidity, and technical surgical factors). (2C)

6.5. Pancreas allocation

As with other organs, there is good evidence that cold ischaemia is detrimental to the outcome of pancreas transplantation in proportion to its duration. The current UK DCD pancreas allocation scheme aims to minimise the distance the pancreas travels to a recipient centre, though this is being reviewed in the light of recent evidence [49].

6.6. Immunosuppression

There are no data that indicate an optimal immunosuppressive

regimen for a DCD pancreas. The immunosuppressive requirements of pancreas transplantation appear to be greater than those of kidney transplantation. Consideration of a kidney-friendly (*i.e.*, low-dose tacrolimus) protocol seems appropriate, with an induction agent such as basiliximab or alemtuzumab followed by mycophenolate and an initial low-dose tacrolimus regimen. Although local immunosuppression protocols will probably continue to vary based on clinical experience and acceptable clinical rejection rates, most UK units currently use alemtuzumab for induction for both DBD and DCD pancreata, whether it is for SPKs or solitary pancreas transplantation. Single-dose alemtuzumab is equally effective as the more commonly used two-dose regimen, as shown by similar pancreas graft rejection rates and survival, and also has the potential to reduce viral and systemic infection rates post-transplant, as suggested by published evidence [50,51].

6.7. Outcomes of DCD donor pancreas transplantation

We recommend that:

- Although arterial and venous thrombosis rates are similar between DCD and DBD pancreata, appropriate systemic anticoagulation protocols should be considered. (1C)

6.8. Novel techniques in pancreas transplantation

We suggest that:

- The pancreas team should stand down after a FWIT of 60 min, unless the pancreas is recovered using NRP, which may allow prolonged warm times. (2C)

NRP has been a major development in recent years [52]. While NRP shows promising improvements in DCD liver transplants, clinical outcomes in pancreas transplantation have not been adequately investigated. The technical feasibility of this technique followed by the successful transplantation of abdominal organs was demonstrated in a landmark UK study, which included two cases of SPK transplants with primary kidney and pancreatic function without adverse events [53].

Experience from a single centre, comparing standard DCD *vs* NRP DCD pancreata, showed that NRP provides at least comparable outcomes [54]. This might be due to the careful selection of DCD donors who proceed to pancreas transplantation, where substantial benefits in clinical outcomes would be harder to obtain. Whether NRP could allow better utilisation of more "marginal" DCD pancreata remains to be seen. It is hoped this question will be answered with future studies.

7. Islet transplantation

7.1. DCD islet donor selection

We suggest that:

- Satisfactory functional islet preparations can be routinely obtained from DCD donors and are as functional *in vitro* and after clinical transplantation as DBD islets. (2B)

Table 2 Summarises the recommendations for DCD donor selection in the UK.

7.2. Islet allocation

We suggest that:

- A pancreas recovered from a DCD donor should be allocated for islet isolation through the National Pancreas Offering Scheme. (2B)

Table 2
Recommended DCD donor islet donor.

Standard criteria donors (SCD)	ECD	Contraindications*
Age 18–45 yr Weight 60–100 kg BMI 21–35 kg/m^2 Cold ischaemia time < 8 h FWIT <30 min	Age < 18 yr or > 50 yr Weight 40–60 or > 100 kg BMI 36–40 kg/m^2 Cold ischaemia >8 h FWIT 30–60 min Retrieval damage (parenchymal/duct transection/traumatic capsular damage)	Age > 65 yr BMI >40 kg/m^2 Cold ischaemia >12 h FWIT >60 min Diabetes mellitus Evidence of pancreatic disease (*e.g.*, chronic pancreatitis) Positive for HCV, HIV, HBV Variant CJD Untreated systemic infection Malignancy, myeloma, lymphoma, leukaemia Invasive cancer in the last 3 years, excluding non-melanoma skin cancer and primary brain tumour

* Absolute contraindications are generally the same as those advised by NHSBT and those outlined in SaBTO guidelines.

Organs for islet isolation and transplantation should be allocated through the National Pancreas Offering Scheme. Current allocation arrangements in the UK may be found on the NHSBT website https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/28334/pol199.pdf.

7.3. Islet donor warm ischaemic times

It is recommended that FWIT is kept below 30 min. The Leiden group recently published their outcomes from 126 DCD category 3 islet isolations [55]. The average FWIT was 23.2 min (+/− 6.4 SD) and although islet yields were slightly lower when compared to DBD donors, functional outcomes following transplantation were no different. After multivariate analysis no significant correlations were found between different warm ischemia periods and islet yield within their data set (FWIT range approximately 10–40 min). The Belgian group analysed 141 DCD category 3 islet isolations and again found no overall correlation between islet yield and total WIT but found that asystolic times >10 min were associated with lower yields and poorer function (measured by insulin content) (12).

7.4. Islet retrieval and preservation

Human islets are very intolerant to prolonged periods of both warm and cold ischaemia. It is important that pancreas retrieval for islet transplantation is performed to the same high standard as for whole pancreas transplantation, cooling the donor organs as rapidly as possible during the retrieval process. As with pancreases for solid organ transplantation, *in situ* perfusion with preservation fluid should be *via* the aorta only (with additional perfusion of the liver *via* the portal vein being instituted by opening the portal vein without impeding venous drainage from the pancreas).

Care should be taken to avoid capsular and parenchymal damage and haematomas as they can adversely affect the islet isolation procedure and success especially if damage is extensive. If there is aberrant anatomy that precludes the use of the pancreas for solid organ transplant, the pancreas can still be used for islets providing the pancreas has not been damaged during the recovery process. If the pancreas is to be used for islet isolation extra vessels are not required.

7.5. In situ and ex situ machine perfusion

NRP is increasingly used in Europe with improved outcomes in liver and kidney transplantation and increased organ utilisation for pancreas transplantation (13). The effect of NRP on pancreas and islet transplant outcomes is less clear but preliminary data in the UK and Europe is encouraging with successful islet transplants having been performed.

7.6. Islet quality assessment

The same quality criteria apply as described in solid organ pancreas transplantation.

7.7. DCD donor islet recipient selection

We suggest that:

- Selection criteria for recipients of islets from DCD donors should be the same as for DBD donors. (2B)

Selection of recipients for islet transplantation from a DCD donor should be the same as for those from DBD donors:

- Insulin-sensitive patients with Type I diabetes and normal renal function who experience recurrent severe hypoglycaemia despite optimised specialist management.
- Insulin-sensitive patients with a renal allograft who are unable to maintain HbA1c <7.0% (53 mmol/mmol) despite optimised specialist management.

There is no evidence that these groups of patients are disadvantaged by receiving islet transplants from a DCD pancreas. Those patients waiting for prolonged periods for second infusions are automatically given priority through the National Pancreas Offering Scheme.

7.8. Immunosuppression

There are no data to indicate an optimal immunosuppressive regimen for DCD islet transplants. The current practice for the small number performed in the UK includes an induction agent such as alemtuzumab or basiliximab, followed by a mycophenolate- and tacrolimus-based maintenance regimen.

7.9. Outcomes

We suggest that:

- There is no difference in the long-term outcome of islet transplants from DCD donors when compared to DBD donors although the comparative cohort is small. (2C)

A series of DCD islet transplants from the Netherlands has demonstrated that although DCD donors resulted in lower yield compared to DBD donors (395,000 *vs* 480,000) there was no demonstrable difference in overall function (AUC C-peptide) during mixed meal tolerance tests and Igls scores [55]. In the UK, data from the King's group have demonstrated that satisfactory functional islet preparations can be routinely obtained from DCD donors [56]. A recent analysis by NHSBT demonstrated that out of 314 islet transplants performed in the UK, 39 have been from DCD donors and there was no statistically significant difference in one-year graft outcome between first routine islet transplants from DCD donors when compared to DBD donors (unpublished data).

Factors that appear to predict good clinical outcomes are: asystolic time < 10 min; FWIT <30 min; short CIT; and donor age < 55 years. There is, however limited data on the long-term outcomes of islet transplants from DCD donors.

8. Discussion

The 2023 UK guidelines on transplantation from deceased donors after circulatory death extends and updates the previous 2013 guidelines [57]. Recipient outcomes after transplantation with organs from DCD donors can compare favourably and even match recipient outcomes after transplantation with organs from DBD donors. Success is dependent upon establishing common practices and accepted protocols that allow the safe sharing of DCD organs and maximise the use of the DCD donor pool. Optimal donor management and careful recipient selection are pivotal to facilitating the donation of as many organs as possible, and it is essential that organ offering systems account for recipient needs and organ utilisation to maximise transplant benefit. It is hoped that these Guidelines will harmonise practice and set the direction for further expansion of DCD organ donation and transplantation in the UK and beyond.

Declaration of Competing Interest

None declared.

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